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### THE PLACE OF PHYSICAL TREATMENTS IN PSYCHIATRY

THE PRESIDENTIAL ADDRESS DELIVERED AT THE ONE HUNDRED AND  
EIGHTEENTH ANNUAL MEETING HELD AT BEXLEY HOSPITAL, 1 JULY, 1958

By

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It is customary and proper that each incoming President of our Association should express his appreciation of the great honour bestowed upon him, and, however eminent he might be, a glance at the names of his illustrious predecessors must have given him a salutary emotion of humility and even apprehension. With me this emotion is all the greater because I feel, in fact I know, that I am a very ordinary fellow compared with those who have preceded me. It is only necessary for me to look back upon the 14 post-war presidents, each of whom I have known well, to realize that I am following a series of men who were not only eminent in one or more branches of psychiatry, but were also great individual personalities. And I wonder if, for once, the *ad hoc* committee did not slip up in their choice. I must say, however, that my apprehensions of failing you would be much greater, were it not for the principal officers of our Association, who are more than capable of carrying a president even of the poorest calibre.

My immediate predecessor, Dr. Armstrong, told us last year that two of his presidential ancestors had been medical superintendents of Littlemore Hospital. I cannot say the same regarding Bexley Hospital (where there have been only three medical superintendents, including myself, during the hospital's 60 years existence), although both my predecessors would have graced the position. I can say, however, that at least five of our most distinguished past presidents, Sir Hubert Bond, Dr. John R. Lord, Dr. Abdy Collins, Dr. A. A. W.

Petrie, and Dr. R. W. Armstrong, served at Bexley during some period of their careers, and I know that all of them had a strong affection for the hospital, where I have worked most happily for the last 23 years.

The first problem of a President-Elect is to decide upon the subject of his Address, and I think he might justifiably be charged with lack of respect for his audience if he did not choose the topic of which he had the greatest knowledge and experience. So, in spite of all temptations to use this opportunity, when I cannot be answered back, to air views on various psychiatric subjects which interest me greatly, but about which I know relatively little, I have chosen "The Place of Physical Treatments in Psychiatry".

This is not the occasion for a critical review of physical treatments; excellent general accounts are to be found in the text-books of Sargant and Slater (1954) and of Kalinowsky and Hoch (1952), while for the more recent developments in chemotherapy there is the review of Funderburk and his colleagues (1956) with its 299 references. What I hope to do is to contrast the mental hospital of 25 to 30 years ago with what it has now become, to discuss how much and in what ways physical treatments have contributed to the changes, and to speculate tentatively upon the future.

To the younger generation of psychiatrists the picture of an ordinary mental hospital before 1937 can only come from imagination, based on hearsay evidence. Even with the help of Dr. Walk I have been unable to find an adequate description of the wards of a British mental hospital between the Wars. Accounts of patients' activities and occupations, and of their gratifying behaviour at social and sporting functions are common, while such things as seclusion, strong clothing, padded rooms, etc., and the regular and thorough stripping and searching of patients are from time to time referred to as inevitable safeguards, but no picture of the ordinary scene in the wards accommodating the more disturbed patients has come to my knowledge. May I, therefore, describe very briefly the picture I saw in June, 1935 on assuming charge of the female side at Bexley Hospital. There were 18 wards in the main building and three outside villas, one of them for new admissions, one for convalescents, and one for the best behaved of the long-standing patients. In the main building two wards only had open doors, five nursed the sick and infirm, two accommodated well-behaved but mainly deluded and unoccupied patients, while in the remaining nine were patients in varying degrees of behaviour disorder. There were two wards of 65 to 70 patients each, composed mainly of chronic melancholics, who had been in the hospital for two to over 20 years. They had lost the sharp edge of their depression, but were anergic, almost inaccessible to stimulation, and preoccupied with delusions of unworthiness, hopelessness and bodily illness which gravely incapacitated them. Some spontaneously remitted, but there were always others to take their places. Even larger numbers of chronic schizophrenics, with far less prospect of remission, occupied the bulk of the other wards. The schizophrenics could be divided into three roughly equal groups: those whose psychosis was, so to speak, "burnt out" and who were occupied in more or less automatic routine work; those who had sunk into a state of apathy and emotional dilapidation; and those who manifested phases of excitement and violence, with noisy, turbulent and destructive behaviour. Even as recently as 1938, 186 patients (this includes the male side) were secluded for the huge total period of 10,580 hours, and no less than 1,430 pounds of paraldehyde and 273 pounds of chloral hydrate were used during the year. In the more refractory wards there was a sustained atmosphere of tension; struggles and minor casualties were numerous, and



there was even an element of personal danger to visitors passing through the wards, especially at meal times.

Nevertheless, I do not want to give the impression that nursing or doctoring in a mental hospital in those days engendered feelings of hopelessness or indifference. Far from it. For various reasons, including a more static population both of patients and staff, a more intensive, integrated community complex existed. Mainly because most nurses and doctors lived in, and there were far fewer extraneous temptations within the geographical and financial orbit of residents, and not least due to the great tradition of the hospital being the centre of service and social life, the staff showed unbounded enthusiasm and affection for their charges, which seemed to increase in proportion to their individual troublesomeness and chronicity. Occupation, which had always been the main plank of therapeutics, was beginning to be more scientifically planned, recreation was systematically organized, and spurts of total-push therapy were already showing what could be done in the most unpromising environment. In many hospitals parole was freely given, as well as day and week-end leave in selected cases. At Bexley on Derby Day two male patients invariably were allowed to get up at dawn and make their own way to Epsom, some 30 miles away. Recently admitted patients remitted spontaneously to the extent that the discharge and death rate pretty evenly balanced the admission rate, but some 95 per cent. of the patients were chronic residents, of whom all but about 2 per cent. were likely to spend the rest of their days in hospital.

Since about 1938 a steady change has occurred, which is accelerating with the years. No doubt several factors share the credit for these changes. In my opinion the most important are (1) the Mental Treatment Act of 1930, (2) the development of out-patient clinics in association with mental hospitals and (3) physical treatments; all of which have made it easier to introduce modern psychiatric concepts.

Although the Mental Treatment Act, authorizing voluntary and temporary patients to be admitted to mental hospitals, came into force in 1930, the stigma enveloping not only the mental hospital patient, but also his whole family, was too deeply rooted to allow the Act to be extensively used for some years. In 1935—five years after the passing of the Bill—only 24 per cent. of admissions to the County and Borough mental hospitals of England and Wales were voluntary patients (Board of Control Report, 1936). Nevertheless, this Act loosened the first guy-rope which was to result in the launching of the mental hospital into the community.

The part played by out-patient clinics, run by mental hospital physicians, cannot be overestimated. Many provincial mental hospitals conducted out-patient clinics at general hospitals well before the War, but this service has increased tremendously since the inception of the National Health Service, especially in London County Council areas. By this means mental hospital doctors have been enabled to see patients at an early stage of their illness, to gain their confidence in a general hospital atmosphere, and, of even more importance, to establish good relationships with the family doctor, whose attitude to the mental hospitals was formerly little less derisive than that of the general public. Domiciliary visiting has been equally propitious in these respects.

The success of physical treatments soon led patients to come into mental hospitals for investigation, followed, if necessary, by a specific course of treatment or an operation, just as occurs in general hospitals; and this, too, tended to lessen the stigma of the mental hospital.



It is true that the earlier years of this century were a period of regression in mental hospital practice, but even in the more enlightened days of the mid-nineteenth century—the heyday of “the moral treatment of the insane”—a liberal attitude towards patients, with all the splendid efforts of the pioneers of those days, could only be applied to a small proportion of patients and in the most progressive of hospitals. Dr. T. P. Rees, in his Presidential Address of 1956, quoted the words of Dr. Hitch of Gloucester, who said in 1841: “In one respect I pride myself in having gone far beyond all other asylum doctors, and that is to the extent to which I trust my patients”, and also, “. . . at least a fifth part of my patients are under no restriction whatever”. If Dr. Hitch had been able to utilize modern physical treatments, I have no doubt that some 90 per cent. of his patients would have been unrestricted, and who knows how much further he would have gone in trusting them?

It is wise and salutary to remind ourselves of what can be done without our modern therapeutic aids and to recall with humility the accomplishments of the humanitarian giants of the past, so long as we do not stifle progress by becoming exclusively *laudatores temporis acti*.

In general I do not think it an overstatement to say that physical treatments have provided our most effective means of rendering the bulk of chronic patients more accessible to social rehabilitation, or that the change in atmosphere of the chronic wards, which I have just described, must be attributed primarily to such procedures as convulsion therapy, leucotomy and, more recently, tranquilizing drugs.

At this point I would like to indicate what I consider the more important contributions of specific treatments. Before the mid-1930s the only physical treatment of more than palliative effect was, of course, the malarial or other pyrexial treatment of G.P.I. This was going strong even when I joined the mental health service in December, 1925, but there were then and for several years to come large numbers of paretics, whose disease had progressed too far to be influenced by the treatment and who exhibited in their final stages, marked by gangrenous trophic ulcers, total incontinence and profound dementia, a sordid and distressing picture, albeit a challenge to the good nurse. As Stoddart (1921), my first teacher in psychiatry, succinctly described the final condition of the general paralytic—“He is bedridden, wet, dirty and oblivious of his surroundings”. I well remember the enthusiasm engendered in the nursing and medical staff by malarial treatment, which created a spirit of cheerful activity in wards oppressed by the hopelessness of such cases.

No major advance in physical treatments in psychiatry occurred until Sakel introduced insulin coma therapy in 1935. This, like malarial treatment, created an atmosphere of therapeutic optimism out of all proportion to the number of patients susceptible to its influence. For here again was something that could and did produce remissions in a condition hitherto therapeutically intractable, although, of course, spontaneous remissions were occasionally seen. The value of I.C.T. has always been controversial, but the considered opinion of psychiatrists who have had lengthy personal experience in its application has been almost universally favourable, and I am convinced that, with judicious selection of patients, it remains a most valuable method.

In 1934 Meduna described his initial work on treating schizophrenics with induced convulsions. By 1937 his method of provoking major fits by intravenous injection of cardiazol had overcome most of its teething troubles, and was started in this country. The fact that Meduna's original rationale proved to be false, that the treatment has turned out to be far more valuable



in affective than in schizophrenic disorders, and that cardiazol has been largely replaced by electrical induction of fits, takes nothing away from the distinction of its originator, to whose imagination and pertinacity we owe, in my opinion, the most far-reaching single factor underlying recent psychiatric progress.

I stress the importance of convulsion treatment, because its effects have been so multifarious and widespread. First of all, it has proved a veritable boon in recent endogenous depressions and in such other states as severe mania, acute puerperal psychoses, severe toxic-confusional states and some fulminating schizophrenic reactions, occasionally preventing death from suicide or exhaustion. Secondly, it has exerted a considerable influence on the morale of prospective patients and their relatives, and, in fact, upon the general public, in providing a therapeutic procedure which not only has proved time and again dramatically successful in severe and most alarming mental illnesses, but has altered the apparently hopeless course of thousands of long-standing psychoses, both schizophrenic and depressive.

Thirdly, without convulsion treatment, the bed problem in mental hospitals might well by now have become insuperable. The Worthing experiment (Carse *et al.*, 1958) has shown how steeply the mental hospital admission rate may fall in districts which have facilities for comprehensive out-patient treatment. Describing this experiment, Carse and his colleagues state that in 1957 the mental hospital admissions from the area embraced by the scheme fell by 324 (59 per cent.) from that of 1956, whereas the admissions from the catchment areas outside the scheme rose by 23 (4 per cent.). Now, in these days of mental hospital overcrowding patients are admitted only when strictly necessary, which means either when their illness is too severe for them to remain outside hospital, or when their home situation is inadequate for their care or is psychologically harmful, or when they require a treatment procedure which cannot be given at home. The existence of excellent day-hospital facilities is likely to preclude admission to any large extent only in those cases where home residence is a practical proposition, and therefore only the third factor is of real importance in releasing hospital beds. It is noteworthy that 317 patients received E.C.T. at the Worthing Clinic during the period in question, and it is fair to presume that nearly all of these would otherwise have been admitted to Graylingwell. Reports from other areas enjoying similar facilities, such as Oldham (Pool, 1958), Sheffield (Thorpe, 1958) and Bolton (Leyberg, 1958), indicate similar results. In these districts, and indeed in many others, large numbers of patients are given E.C.T. as out-patients, and each successful course of out-patient E.C.T. constitutes a bed saved for anything from three weeks to three months.

Lastly, but probably most important of all, has been the effect of convulsion treatment upon disturbed and highly excitable patients. By rendering so many of them quieter and more amenable to re-socializing influences, convulsion treatment undoubtedly played a pioneer role in initiating the opening of the old-time chronic, refractory wards, and in accelerating the major reforms of present-day mental hospital practice. Moreover, without the easing of the nursing burden in this type of ward, many hospitals could not possibly have found enough staff to nurse adequately the steadily increasing numbers of old, infirm patients admitted every year.

The mid-1930s may well be called the golden era of the inception of physical treatments in psychiatry; for while Sakel and Meduna were working on insulin and convulsion treatment respectively, Moniz and Lima in Lisbon were developing the surgical technique to be known as pre-frontal leucotomy.



As long ago as 1889 Burckhardt utilized a form of frontal leucotomy, but this was not followed up and, to quote Kalinowsky and Hoch (1952), "full credit for rescuing Moniz's work from probably the same fate as Burckhardt's earlier attempts goes to W. Freeman, who, together with J. Watts, performed the first such operation in the United States on 14 September, 1936".

Psychosurgery has had a turbulent passage; it has provoked bitter attacks, often emotionally rather than logically derived, and mainly based on the viewpoint that any procedure which might alter the personality, whether for better or worse, is unethical. On that score any educative or psychotherapeutic effort to guide a severely delinquent child into the paths of good citizenship might be equally condemned. More reasonable objections sprang from those cases where excessive brain damage led to irresponsibility and lack of emotional control, which is, in the words of Freeman and Watts (1943), "at times rather trying on the close associates". After 20 years' experience, however, the benefits of psychosurgery can be seen unequivocally to have exceeded the occasional disasters due to undesirable personality changes, especially as they are so seldom permanent. The standard bilateral operation, and other drastic techniques, which alone involve these hazards, should be and largely have been confined to patients with the poorest prognosis, mainly intractable schizophrenics. Even so, with sensible selection, some 20 per cent. of long-standing, severely disturbed schizophrenics can be expected to remit sufficiently to leave hospital, and for the most part to support themselves. In addition, standard leucotomies during the years 1941 to 1954 have been second only to convulsion therapy in changing the atmosphere of the refractory wards in British mental hospitals. During the last 4 years the introduction of tranquillizing chemotherapy has greatly reduced the use of both standard leucotomy and maintenance E.C.T., a topic I shall return to when discussing ataractics.

Modified leucotomies are now largely employed except in severe schizophrenic states, and present far less danger either to life or to the personality. They are particularly valuable in obsessive-rumination states associated with severe tension, the very conditions which provoke the greatest distress and dangers of suicide.

Since 1936 several valuable modifications of existing physical treatments have been introduced, chiefly concerned with convulsion therapy and leucotomy, but no new discovery likely to accelerate the march of psychiatric progress appeared until 1953, when, following the pioneer work of Delay and his colleagues in France, the first of the tranquillizing drugs became at our disposal.

Tranquillizers or ataractics must be differentiated from sedatives. If pushed too far, some of them produce drowsiness, but properly administered the objective in psychiatric practice is to eliminate or diminish psychotic symptoms without reducing the patient to a state of lethargy. Four years' experience of a large number of tranquillizing drugs has taught us that none, so far discovered, is of any comparable value to the barbiturate sedatives in anxiety states, that obsessional symptoms are scarcely influenced at all, and that only the phenothiazine group and the Rauwolfia groups are significantly effective, and then only in certain psychotic conditions. But these two groups have made a definite and deep impression in their particular sphere of influence.

So many wild rumours have emanated from America and other parts of the world to the effect that ataractic therapy was a panacea for practically every type of nervous and mental disorder that I was relieved to find that



Paul Hoch, whose domain embraces all the 105,000 patients of the New York State Mental Hospitals, shared the conclusions of well-informed opinion in this country. In his opinion (Hoch, 1958) "chlorpromazine is probably the most effective drug in our hands in the treatment of psychotic patients", with reserpine the next best, while "other available compounds such as Frenquel and Miltown are far less effective". It is noteworthy that the patient population of the New York State mental hospitals increased each year from 1946 to 1955 (inclusive) by a yearly average of over 2,000, while during the three years ending March, 1956, 1957 and 1958, the population, instead of showing a further rise, actually fell by 452, 453 and 1,200 patients in each respective year (Brill and Patton, 1957; Brill, 1958). Hoch attributes this dramatic fall almost entirely to the effects of chlorpromazine and reserpine.

In British mental hospitals there has been the same kind of result, but on a much smaller scale, and I think it is fair to say that the impact of tranquillizing chemotherapy in any hospital varies inversely with the efficiency of its previous utilization of E.C.T., leucotomy and rehabilitation programmes. But even where the utmost use of all available treatments had been in force, the phenothiazine and Rauwolfia tranquillizers have brought about changes of real significance. To summarize the present situation, one can say that ataractics of these two groups, judiciously administered, are often successful in eliminating or diminishing such symptoms as restlessness and excitement, aggressiveness, destructiveness, agitation, faulty habits, hallucinations and delusions, occurring in a psychotic setting. They are effective in both recent and long-standing states of schizophrenia and paraphrenia, mania and agitated depression, and tend to diminish the motor and psychotic over-activity so often a disturbing feature in senile and other organic psychoses. In long-standing psychoses, chiefly schizophrenic, most encouraging results have been obtained. Many patients of the poorest prognosis have become quiet, co-operative, friendly and well-behaved, while more than a few have made good remissions. Most of these, at any rate at Bexley, had previously had courses of E.C.T. with only transient benefit, and some had undergone leucotomy. I would say that some 35-40 per cent. of chronic schizophrenics with disturbed conduct are likely to improve to an extent which is incontrovertible, and needs no rating scales to establish. Some 5 per cent. can be expected to become symptom-free, and many more than that get well enough for discharge, if adequate home care is available. The need for maintenance courses of E.C.T. has been substantially reduced, although by no means abolished. A few modified convulsions remain the quickest and surest way of aborting outbreaks of disturbed and disturbing behaviour, and some schizophrenics respond far better to E.C.T. than to ataractics.

To what extent chemotherapy will supersede standard leucotomy in the treatment of schizophrenia is at present hard to say. Certainly much fewer standard leucotomies have been done in Britain and the United States since tranquillizing drugs were introduced. There is no doubt that most long-standing aggressive, noisy and troublesome schizophrenics are benefited by chlorpromazine or reserpine, or by a combination of both, but whether some of these would have made a fuller remission after leucotomy is an open question. The situation is equally problematical in more recent cases. If insulin coma treatment and convulsion treatment have produced only temporary benefit, and tranquillizers have removed the more severe symptoms, leaving a schizophrenic residue, should leucotomy be performed, and if so should it be a modified or a standard operation?



This leads to other interesting questions. The great majority of chronic schizophrenics who have made a good remission under tranquillizers, eventually relapse, if they stop taking the drug, although perhaps not for many months or even longer. Should we endeavour to keep them indefinitely on a small maintenance dose—often a difficult task—or should we stop treatment after 6–12 months of remission, hoping against hope that some will remain permanently well? We do not yet know whether ataractics can succeed in preventing further attacks of mania or schizophrenia in the recurrent forms of these disorders. Evidence on this point is scanty, partly because patients all too often omit their tablets after feeling quite well for several months, but what evidence there is points to a better prophylactic effect in schizophrenia than in mania.

Lastly, will tranquillizing drugs, with or without E.C.T., take the place of insulin coma treatment? I do not believe the time has yet come to jettison I.C.T., but I hope, and think, that all the more drastic physical methods, including leucotomy, I.C.T. and convulsion treatment, will eventually be superseded, as we learn more about the chemical changes underlying the production of psychotic pictures, and are able to adapt chemotherapy in the light of further research findings.

While pointing out how much we owe to physical treatments in psychiatry, I am very much aware that they are at times employed unnecessarily and even harmfully. Intensive application of E.C.T. is occasionally a life-saving measure, but this is no valid reason for slugging neurotics into a punch-drunk state of confusion by multiple convulsions, nor can I approve the wholesale leucotomy programmes practised in the past at one or two hospitals on practically all schizophrenics, irrespective of clinical picture. Indiscriminate use of ataractics can easily render a hospital population so lethargic as to justify the accusation that we are merely resurrecting the old paraldehyde-drenched wards, without the smell. Unfortunately, any successful and relatively simple method of treatment constitutes a temptation not easy to resist, especially when relatives are clamouring for something to be done. The leading exponents of these treatments realize and deplore their promiscuous use, for Sargant and Slater (1954) state on the first page of the introduction to their well-known text-book, "the trouble is that these treatments may be tried out in an indiscriminate manner", and those with the most experience of tranquillizing drugs have been the first to protest against their misuse, as was evident at the Annual Meeting of the British Medical Association in July, 1957.

I have not intended to make an apologia for physical treatments in psychiatry; in any case that is unnecessary. Rather do I want to make an emphatic plea for abolishing prejudice and petty-mindedness, when considering any form of treatment. The welfare and happiness of the patient and his relatives must outweigh all theoretical considerations and personal predilections. Adolph Meyer's multidimensional approach to the study of each patient is only of real value if extended to treatment, which is not always borne in mind even by devout Meyerians.

In 1940 at this hospital much was done, by habit training and intensive group methods alone, to uplift some of the most deteriorated patients. It was an arduous task with gratifying but only limited achievements, patients tending to fall back without continuous stimulation, which inevitably flagged as enthusiasm gradually burnt itself out. On the other hand, to use physical treatments alone, without the aid of psychotherapeutic, social



and occupational measures, is tantamount to amputating a leg without afterwards supplying a crutch or artificial limb. Only by intelligent integration of the various procedures at our disposal can we expect to get the best results.

Nobody likes the physical treatments in psychiatry: they are cumbersome, often lengthy, and have their dangers, but when selected and administered with thoughtfulness and care, their failures and occasional disasters are infinitesimal compared with the benefits they bring. That the future will abolish the more mechanistic of the physical treatments I have little doubt, and still less that prevention, at least in the so-called functional psychoses, will in the end largely obviate the need for treatment.

This leads me to speculate for a moment upon the future. For some time the accent has been on mental hygiene, but so far prophylaxis has not extended appreciably beyond the sociological field. I have no doubt that metabolic and physiological (including electro-physiological) researches, which have already helped us to open many doors in mental hospitals, will in the next decade unlock even more metaphorical doors concealing the secrets of psychiatric aetiology. Taking, as an example, the greatest scourge in our field, schizophrenia, we have a condition, or series of conditions, in which at least five aetiological factors are involved—genetic, constitutional, endocrinological, metabolic and environmental. Whatever the primary cause or causes may be, the final pathway seems to lie along biochemical routes. The work of Gellhorn (1943, 1953) on the regulation of the autonomic nervous system, the effects of sympathin, of the hallucinogens and of serotonin upon synaptic inhibition, and the work of Osmond, Hoffer and Smythies (1952, 1954) on adrenochrome, to mention but a few of recent research trends, all point to this.

I think it most likely that the first really effective prophylactic methods against schizophrenia, and some other psychoses, will be in the nature of chemical antagonizers to the faulty metabolic patterns which precipitate the clinical picture. It should be possible with further knowledge to prevent the development of the psychotic stage, and perhaps, by prophylactic treatment in childhood, where the infantile pre-schizoid developmental pattern, described by Bender (1947, 1953) and her followers (Fish, 1957), exists, even to prevent the development of schizoid personalities. If this comes to pass the mental hospital may eventually consist of a small early treatment centre, an even smaller department for intractable psychoses and, I am afraid, a much larger section employed in caring for senile and other organic states.

The year 1956 gave us two stimulating addresses. Both Dr. J. R. Rees, in his Maudsley Lecture on "Psychiatry and Public Health" and Dr. T. P. Rees, in his Presidential Address entitled "Back to Moral Treatment", stressed the immense importance of preventive psychiatry in relation to public health and community life. My thesis is somewhat narrower, but is an essential accessory to theirs.

The key to future treatment lies in prevention; and the key to prevention in the harmonious union of physical and psychological research.

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# LEONHARD'S CLASSIFICATION OF SCHIZOPHRENIA

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## A. INTRODUCTION

JASPERS (1946) has pointed out that in the history of psychiatry one can distinguish two main types of psychiatrist. On the one hand there is the describer who depicts a lively clear clinical picture and communicates it to the reader in everyday speech. On the other hand there is the analyst who dissects the clinical picture and tries to obtain clear concepts about the abnormal phenomena. The describer is always popular because little effort is required to understand his views and appreciate his clinical descriptions. However it is much more difficult to understand the analyst as this requires time-consuming preparatory work and an attempt to apply the analyst's views in practice. Thus anyone who wishes to understand the views of Kleist and Leonhard, who are the modern representatives of the great clinical analyst Carl Wernicke, has a difficult task. If therefore this present communication appears to disagree with other work recently published by the author (Fish, 1957b, 1958) then all that can be said in extenuation is that the analysis of clinical pictures is difficult and one can only achieve accuracy in this field by learning from mistakes.

The author in a previous communication has outlined the views of Kleist and his co-workers on the classification of schizophrenia (Fish, 1957a). It may have appeared from that communication that Leonhard agreed entirely with Kleist. This in fact, is not so. Although Leonhard's views are similar in some respects, his classification of schizophrenia is less cumbersome and his clinical descriptions are more precise. He originally investigated schizophrenics who had been ill for longer than ten years, because he believed that the clinical picture would be more stable in such patients. He investigated 530 chronic schizophrenics in the Gabersee Mental Hospital and the Erlangen Nerve Clinic and Mental Hospital. He published his results in a monograph in 1936 (Leonhard, 1936). He divided chronic schizophrenia into systematic and nonsystematic groups. The systematic group he further subdivided into six catatonic, two hebephrenic and six paranoid subgroups. He then joined Professor Kleist in Frankfurt and took part in the follow-up studies on schizophrenia carried out by Professor Kleist and his pupils. Leonhard continued to develop and modify his ideas on the classification of schizophrenia and published a series of communications (Leonhard, 1942 a and b, 1943 a and b, 1944 a and b) which owing to World War II are not readily available in Britain. He has now published his views in book form (Leonhard, 1957).

Leonhard has retained the broad division of schizophrenias into systematic and nonsystematic groups. In the systematic group one system in the central nervous system is believed to be involved by the disease process in the case of the simple systematic forms. In the case of the combined syste-

matic forms two such systems are involved. In nonsystematic schizophrenias the disease process is believed to involve several systems in the central nervous system and is also not primarily a disease of the nervous system. Leonhard is very precise about the symptomatology of the systematic schizophrenias. He describes in detail the groups of symptoms which are characteristic of each subgroup. He does not recognize a separate main group of speech and thought confused schizophrenias. His scheme is thus less cumbersome than that of Kleist but it is in some ways more precise. In practice because of the more precise description of symptoms it is also much easier to use.

Unfortunately the more recent views of Leonhard were not fully known to the author when he began to investigate a series of chronic schizophrenics in 1955. An attempt was made to classify these patients according to Leonhard's earlier views. This was not possible as a large number of cases were found to be unclassifiable. In view of the fact that Kleist's views were more readily accessible this series was classified according to Kleist's scheme (Fish, 1958). Since this was done the author has been able to study Leonhard's views more closely. He has also had the good fortune to discuss the matter with Dr. Christian Astrup of Oslo, Norway, who has classified 122 chronic schizophrenic patients according to Leonhard's scheme (Astrup, 1957). During his recent stay in England, Dr. Astrup and the author reviewed the author's original series of chronic schizophrenics. They were able to examine jointly all but eight of these cases and classify them according to Leonhard's scheme. Four additional cases were also seen which had been excluded from the previous series because of inadequate investigation. The author carefully considered the protocols of the eight cases which could not be seen jointly and he was able to classify them according to Leonhard's scheme. All these 111 female patients who had suffered from schizophrenia for more than ten years could be classified according to Leonhard's criteria without too much difficulty. The distribution of these cases among the various subgroups is shown in Table 1.

## B. THE NON-SYSTEMATIC SCHIZOPHRENIAS

Leonhard considers that earlier authors were wrong when they grouped together all psychological illnesses which ended in a defect state and called them schizophrenia. He believes that the systematic schizophrenias are quite different from the nonsystematic schizophrenias. Like Kleist he separates off from schizophrenia a group of psychoses which show symptoms which other authors consider to be schizophrenic (Schneider, 1955), but which have a favourable outcome. Kleist, following Schröder, originally called these psychoses degeneration psychoses but later he used the term cycloid marginal psychoses (Cycloide Randpsychosen); Leonhard calls these illnesses cycloid psychoses.

These cycloid psychoses, which are three in number, are the anxiety-happiness psychosis, the excited-inhibited confused psychosis and the hyperkinetic-akinetic motility psychosis. These psychoses are bipolar in that opposite groups of symptoms may appear at the same time or at different stages of the illness. Thus in anxiety-happiness psychosis there may be an anxious unpleasant mood with ideas of self reference, hypochondriasis, ideas of inferiority, sense deceptions and ideas of influence. On the other hand there may be an exalted mood with ideas of inspiration which are associated with



TABLE I

|                                           |    |    |    |    |    | Cases |
|-------------------------------------------|----|----|----|----|----|-------|
| A. NONSYSTEMATIC SCHIZOPHRENIAS           |    |    |    |    |    | 16    |
| 1. Affect laden Paraphrenia               | .. | .. | .. | .. | .. | 5     |
| 2. Schizophasia                           | .. | .. | .. | .. | .. | 8     |
| 3. Periodic Catatonia                     | .. | .. | .. | .. | .. | 3     |
| B. SIMPLE SYSTEMATIC SCHIZOPHRENIAS       |    |    |    |    |    |       |
| 1. <i>Catatonic Forms</i>                 | .. | .. | .. | .. | .. | 22    |
| (a) Parakinetic Catatonia                 | .. | .. | .. | .. | .. | 5     |
| (b) Manneristic Catatonia                 | .. | .. | .. | .. | .. | 2     |
| (c) Proskinetik Catatonia                 | .. | .. | .. | .. | .. | 3     |
| (d) Negativistic Catatonia                | .. | .. | .. | .. | .. | 0     |
| (e) Speech-prompt Catatonia               | .. | .. | .. | .. | .. | 3     |
| (f) Speech-inactive Catatonia             | .. | .. | .. | .. | .. | 9     |
| 2. <i>Hebephrenic Forms</i>               | .. | .. | .. | .. | .. | 16    |
| (a) Silly Hebephrenia                     | .. | .. | .. | .. | .. | 2     |
| (b) Eccentric Hebephrenia                 | .. | .. | .. | .. | .. | 7     |
| (c) Shallow Hebephrenia                   | .. | .. | .. | .. | .. | 2     |
| (d) Autistic Hebephrenia                  | .. | .. | .. | .. | .. | 5     |
| 3. <i>Paranoid Forms</i>                  | .. | .. | .. | .. | .. | 41    |
| (a) Hypochondriacal Paraphrenia           | .. | .. | .. | .. | .. | 7     |
| (b) Phonemic Paraphrenia                  | .. | .. | .. | .. | .. | 12    |
| (c) Incoherent Paraphrenia                | .. | .. | .. | .. | .. | 10    |
| (d) Fantastic Paraphrenia                 | .. | .. | .. | .. | .. | 9     |
| (e) Confabulatory Paraphrenia             | .. | .. | .. | .. | .. | 3     |
| (f) Expansive Paraphrenia                 | .. | .. | .. | .. | .. | 0     |
| C. COMBINED SYSTEMATIC SCHIZOPHRENIA      |    |    |    |    |    |       |
| 1. <i>Catatonic Forms</i>                 | .. | .. | .. | .. | .. | 6     |
| (a) Manneristic-proskinetik catatonia     | .. | .. | .. | .. | .. | 1     |
| (b) Manneristic-speech prompt catatonia   | .. | .. | .. | .. | .. | 2     |
| (c) Proskinetik-speech inactive catatonia | .. | .. | .. | .. | .. | 3     |
| 2. <i>Hebephrenic Forms</i>               | .. | .. | .. | .. | .. | 3     |
| (a) Silly Eccentric Hebephrenia           | .. | .. | .. | .. | .. | 2     |
| (b) Silly Shallow Hebephrenia             | .. | .. | .. | .. | .. | 1     |
| 3. <i>Paranoid Forms</i>                  | .. | .. | .. | .. | .. | 7     |
| (a) Phonemic-fantastic Paraphrenia        | .. | .. | .. | .. | .. | 3     |
| (b) Phonemic-confabulating Paraphrenia    | .. | .. | .. | .. | .. | 1     |
| (c) Fantastic-incoherent Paraphrenia      | .. | .. | .. | .. | .. | 3     |

hypochondriasis, ideas of reference and sense deceptions. In the excited inhibited confused psychosis there are phases of excitement and inhibition. In the excited phases there is pressure of speech with incoherence. Misidentification of persons, ideas of reference and auditory hallucinations may occur in such phases. Perplexity occurs in the inhibited phases often together with ideas of reference and significance and less often in association with auditory hallucinations. The hyperkinetic-akinetic motility psychosis has an excited and an inhibited phase. The excited phases consist of a purposeless hyperkinesia, while in the inhibited phase all forms of movement are restricted but reactive and expressive movements are affected before the purely voluntary movements.

These cycloid psychoses are similar to the "degeneration psychoses" of Kleist. Leonhard claims that they are clinical entities which can be isolated on clinical and genetic grounds. Other authors would, of course, regard these illnesses as abortive forms of schizophrenia (Mayer-Gross, Slater, Roth, 1955).

The main reason for discussing the cycloid psychoses here is that Leonhard believes that the nonsystematic schizophrenias are more closely related

to cycloid psychoses than they are to the systematic schizophrenias. He relates each variety of cycloid psychosis to a variety of nonsystematic schizophrenia which he divides into affect-laden paraphrenia, schizophasia and periodic catatonia. Thus he considers that anxiety-happiness psychosis is related to affect-laden paraphrenia, motility psychosis to periodic catatonia and confused psychosis to schizophasia. The differential diagnosis of the cycloid psychosis from the nonsystematic schizophrenias may be difficult but Leonhard claims that there is no difficulty in distinguishing between a systematic and a nonsystematic schizophrenia. The systematic forms run a slowly progressive course whereas the nonsystematic forms may remit or show a clearly periodic course. Thus in some cases periodic catatonia may present like an affective disorder for several attacks before it declares itself to be catatonic. The symptomatology also distinguishes the two forms of schizophrenia in that bipolarity of symptomatology is found in the nonsystematic schizophrenias.

It will be seen that although both Kleist and Leonhard subdivide schizophrenia into systematic and nonsystematic groups their views on nonsystematic schizophrenias do not coincide. One could with some justification equate affect-laden paraphrenia with Kleist's progressive reference psychosis, schizophasia with his atypical confused schizophrenia and periodic catatonia with his iterative catatonia. However this would not do justice to Leonhard because his delineation of the nonsystematic forms is much more precise than that of Kleist.

### 1. AFFECT-LADEN PARAPHRENIA

This illness is distinguished by the affective loading of the paranoid delusions. These patients talk about their delusions with irritation or enthusiasm. In the systematic paranoid schizophrenias the delusions have no such affective loading. Often the patient does not become upset when one laughs at his delusions and if he does become emotionally disturbed it is only for a short time and the disturbance soon passes away. This does not occur in affect-laden paraphrenia where the more one denies the patient's delusions the more upset he will become. These patients may shout, scold and threaten when their beliefs are treated discourteously.

At the onset of the illness severe affective swings into anxiety or ecstasy often occur and may continue as the psychosis progresses. These affective changes are always associated with the formation of delusional ideas. In anxiety ideas of self reference occur together with auditory hallucinations, while in ecstasy ideas of happiness occur in association with visions and auditory hallucinations. In the beginning it may be difficult to distinguish this psychosis from anxiety-happiness psychosis but as the illness progresses the distinction becomes clear. In particular, it becomes more and more obvious that the delusions and sense deceptions cannot be entirely understood as arising from the abnormal affect. These paranoid phenomena take on illogical and incomprehensible forms. Thus the abnormal body sensations in affect-laden paraphrenia have a completely hallucinatory character because they are connected with outside influences. On the other hand in anxiety-happiness psychosis these sensations can be understood as arising from the abnormal affective state. The clinical picture at the onset of affect-laden paraphrenia is that of anxiety with ideas of reference but sometimes one finds a more hostile attitude to the environment when the patient is irritated and has ideas of reference. This corresponds to the "progressive reference psychosis" of Kleist.



The degree of systemization of the delusions varies from case to case, sometimes they may be well systematized and the clinical picture may be that which Kraepelin designated as paranoia. Because of the bipolar nature of the affect, delusions of persecution and happiness may occur together. Often the delusions become more and more illogical and finally a fantastic delusional system may occur. In this there are extravagant grandiose ideas, misidentifications of people, memory falsifications, absurd ideas and hallucinations in all the sensory fields. These symptoms are somewhat similar to those occurring in the systematic form known as fantastic paraphrenia, but they are rarely completely expressed in affect-laden paraphrenia where some of these fantastic symptoms can be absent while others dominate the clinical picture. Apart from this the affective loading of the delusions is very obvious in affect-laden paraphrenia and if it is not apparent at first sight, it will become so as the patient is stimulated.

Catatonic and schizophrenic symptoms may be found in this illness. Catatonic illnesses are sometimes found in the relations of patients with affect-laden paraphrenia.

In the author's series five cases were considered to be affect-laden paraphrenia. One of these was W.M.D., who in a previous communication (Fish, 1958) was classified as a combination of Verbal Hallucinosis and Phantasio-phrenia.

Leonhard finds the genetic loading to be higher in the nonsystematic schizophrenics than in the systematic schizophrenics. Thus he found the frequency of schizophrenia among the parents of affect-laden paraphrenia to be 6.7 per cent.

In the author's series one patient had an uncle who had died in a mental hospital but his records were untraceable and another had a grossly abnormal mother who believed in the patient's persecutory delusions.

## 2. SCHIZOPHASIA

Kraepelin described schizophasia as a variety of schizophrenia in which there was gross confusion of speech so that the patient's speech was completely unintelligible. This gross confusion contrasted with the patient's fairly well ordered behaviour and ability to work and make social contact (Kraepelin, 1919). Leonhard has investigated the relatives of schizophrenic patients and found that schizophrenic illnesses in these relatives are rarely pure schizophasias since catatonic and paraphrenic features are frequently found.

He stresses the relationship between schizophasia and the confused psychosis. However the morbid phenomena in schizophasia are much more pronounced. He suggests that this relationship with the confused psychosis accounts for the fact that schizophasia occurs in two forms. In schizophasia in Kraepelin's sense there is severe confusion of speech and pressure of speech with many grammatical mistakes but few neologisms. In the other kind of schizophasia the patient is lacking in drive, the speech confusion is more restricted and neologisms are more common. This type of schizophasia is more likely to occur if there are catatonic features. Leonhard points out that these different forms of schizophasia could be understood in relation to the excited and inhibited poles of the confused psychosis. The thought confused excited patient being the classical schizophrenic and the thought confused inhibited patient being the other type. However he claims that the two different forms often occur in the same family and therefore cannot be considered to be genetically distinct disorders.

Leonhard finds a high genetic loading in schizophasia. In his series the incidence of schizophrenia in the parents was 20.6 per cent.

In the author's series there were 8 cases of schizophasia. One of these, I.M., has been described in a previous communication (Fish, 1958). In all 8 cases there was evidence of psychiatric disorder in the family. In four cases there was a history of suicide of a close relative. In two cases a brother committed suicide, in one case a maternal uncle and in one case the father had murdered his wife and child and committed suicide. In four cases there was a history of mental hospital admission of a close relative. In one case a maternal uncle had died in a mental hospital but his clinical notes were untraceable. In one case the patient's father was in hospital and had schizophasia, in another the patient's brother had a schizophasic illness and in a third the clinical notes of a paternal uncle who died in St. George's Hospital, Morpeth, suggested gross speech confusion.

### 3. PERIODIC CATATONIA

For Leonhard this is a catatonic illness in which remissions regularly occur and in which there is usually an admixture of hyperkinetic and akinetic symptoms. Hyperkinesia acquires a certain degree of rigidity because of the admixture of akinetic features. Thus movements tend to proceed in a stiff jerky manner and the natural grace of the movements is absent because the harmonious interplay of the individual motor acts does not occur. Because of this distortion of motor activity the meaning of movements is lost so that reactive and expressive movements lose their meaning. Thus gestures become vague indefinite movements and facial expressions become grimaces. Excitements which occur in periodic catatonia are parakinetic because of this modification of the natural course of motor acts. When these patients are akinetic an aimless movement of an extremity often occurs which generally becomes uniform and may be a stereotypy or an iteration. Thus stereotypy occurs despite the general postural rigidity and the rigidity of mimic expression. In spite of the impoverishment of movement the patients, when akinetic, often repeatedly take on definite postures and have postural stereotypies. Leonhard considers that the admixture of hyperkinetic and akinetic features can also be seen in impulsive actions and in negative behaviour in states where the patient has a poverty of movement. Uniformity of motor performance in catatonia is also considered to be in favour of a diagnosis of periodic catatonia.

Leonhard considers that the motility psychosis is related to this illness but in the motility psychosis hyperkinesia and akinesia do not occur together but alternate and on the whole the symptoms are less severe.

Although remissions occur after the acute shifts permanent defect finally occurs. This is likely to occur more rapidly after attacks of akinesia than after hyperkinesia. Leonhard divides these defects into mild, moderate and severe which he designates as states of psychic lameness, dullness and stupidity respectively. In the severe defect of stupidity there is a degree of deterioration which is reminiscent of organic disease. In these defect states there is an impoverishment of drive but impulsive excitements are frequent and excitements due to irritability also occur. These excitements can take on a negativistic character.

If the illness is mild it may mimic a motility psychosis both in the symptomatology and in the course of the illness. Symptoms of schizophasia or affect-laden paraphrenia may be present at some time in the illness.



The genetic loading in periodic catatonia is much greater than in the systematic forms of schizophrenia. Leonhard found that the psychiatric illnesses among relatives of patients with periodic catatonia were usually clearly of the nature of periodic catatonia both as regards the symptoms and the course of the illness.

In the author's series three cases were classified as periodic catatonia but no patient had a family history of mental illness.

#### 4. THE VALUE OF LEONHARD'S CONCEPT OF NONSYSTEMATIC SCHIZOPHRENIA

The author in his work of classification found that Leonhard's descriptions of these illnesses were easy to follow and it was much easier to classify according to Leonhard's descriptions than according to Kleist's. Some cases which the author previously considered to be combined systematic paranoid forms (Fish, 1957b, Fish, 1958) were easily classified as affect-laden paraphrenia whereas from Kleist's vaguer descriptions (Kleist, 1949) it was not possible to classify them as progressive reference psychoses. Similarly Leonhard's concept of schizophasia seemed to be much more useful clinically than Kleist's concept of confused schizophrenias with its large number of subgroups. However the diagnosis of periodic catatonia was mainly made by the author in a negative way, that is the cases did not fit into the typical catatonic subgroups or combinations of them.

#### C. SYSTEMATIC SCHIZOPHRENIAS

In the nonsystematic schizophrenias the symptoms tend to be polymorphous and because of the diversity of symptoms it is difficult to outline the clinical pictures very sharply. In the systematic schizophrenias the opposite is true because the symptomatology is clear cut and the clinical pictures unequivocal.

Leonhard believes that specific circumscribed functional fields are affected in the systematic schizophrenias so that in each subform a definite higher function of the nervous system is involved. If this is so, then investigations of the systematic schizophrenias will lead to an understanding of the higher functions of the nervous system.

These sharply delimited clinical pictures of systematic schizophrenia are found in the end states of schizophrenia. Earlier in the illness non-specific effects of the morbid process or environmental pathoplastic factors may be intermixed with the defect symptoms so that the illness is difficult to classify. As a general rule the onset of the illness in the systematic group is gradual, whereas an acute stormy onset is more likely in the nonsystematic group, but may also be present in the combined systematic forms. Despite the difficulty in classifying the illnesses in the early stages it is much easier to do so once the observer has learned to recognize the typical schizophrenic end states.

#### D. SIMPLE SYSTEMATIC SCHIZOPHRENIAS

In the majority of systematic schizophrenias only one psychic system is affected and these are called simple systematic schizophrenias. Leonhard stresses that it is not a question of the presence of individual symptoms in these simple systematic forms but of characteristic combinations of symptoms. For example a given case is a phonemic paraphrenia not because auditory hallucinations are very prominent but because there is a special variety of

auditory hallucination, a characteristic affectivity and thought disorder. Again phonemic and hypochondriacal paraphrenia differ because bodily hallucinations occur in one and not in the other but it is just as important that the basic mood is quite different. Thus one must always identify a very specific combination of symptoms before a diagnosis can be made.

### 1. THE CATATONIC FORMS

Leonhard believes that the systematic nature of these schizophrenic illnesses is best seen in the catatonias. Systems which are at a slightly higher level in the nervous system than those involved in neurological system illnesses appear to be affected in these illnesses. In systematic catatonias three pairs of illnesses can be recognized. Leonhard suggests that higher functions of the nervous system are regulated by reciprocating system pairs which balance one another. Affections of one or the other member of a system pair will thus produce contrasting illnesses. Two forms of catatonia appear to be peripheral in that the symptomatology is very similar to that of neurological illnesses. Thus parakinetic catatonia resembles chorea and manneristic catatonia paralysis agitans. Leonhard postulates that these two catatonic forms are due to disorders of a system pair which is responsible for motor function and is only one stage higher than the function involved in chorea and paralysis agitans. For Leonhard paired opposed illnesses, due to disorder of system pairs guaranteeing functions, are to be found not only in the catatonias but also in the hebephrenias and paraphrenias.

Leonhard classifies the systematic catatonic illnesses into:

- (a) Parakinetic Catatonia.
- (b) Manneristic Catatonia.
- (c) Proskinetik Catatonia.
- (d) Negativistic Catatonia.
- (e) Speech-prompt Catatonia.
- (f) Speech-inactive Catatonia.

#### (a) *Parakinetic Catatonia*

This form has been described by Kleist (Kleist, 1943, Fish, 1957) but Leonhard points out that Kleist applied this term to acute cases as well as chronic. Leonhard's concept of this form is that it is slowly progressive and the parakinetic movements slowly set in, so that at the onset they are not striking but may easily be overlooked. For Leonhard patients with marked parakinesia on the background of a general motor excitement are usually examples of periodic catatonia.

The hyperkinesia may only become pronounced when the patient is stimulated. All voluntary actions are carried out in an unnatural awkward way and involuntary movements are jerky and reminiscent of choreiform movements. Motor activity seems to be broken down into its constituent movements and the smooth transition from one individual movement to the next is absent. The involuntary movements which occur seem to be distorted reactive and pseudo-expressive movements. Facial movements are especially affected and these patients often grimace a good deal. Speech is affected by the motor disorder so that these patients speak in short sharp utterances and the words appear to be cut up. The sentences are usually short and ungrammatical. Sometimes these patients make remarks which are to the point, but at other times their remarks seem to be fortuitous and irrelevant. Leonhard



found a comparatively heavy genetic loading in these patients and where sufficient details of the psychiatric illness of the relatives were available the diagnosis was usually parakinetic catatonia.

In the author's series five patients were classified as parakinetic catatonia and in two there was a family history of mental hospital admissions. In one case the maternal grandmother had been in a mental hospital and in the other a maternal uncle. Unfortunately the case notes of these relatives were untraceable.

#### (b) *Manneristic Catatonia*

Leonhard originally called this form rigid catatonia because he first observed severe cases. This form of Leonhard's corresponds to Kleist's stereotyped or manneristic catatonia. At the onset of the illness, mannerisms occur but as the illness progresses all involuntary movement becomes less and less. As a result posture and movement become stiff. With the progress of the illness motor activity becomes increasingly stereotyped and this may result in the whole of a day's activity being carried out in a fixed manneristic way. As the impoverishment of movement becomes more pronounced mannerisms of commission become replaced by mannerisms of omission. Thus the patient tends to have stereotyped attitudes, a stiff facial expression, mannerisms of food refusal or refusal to go to the toilet.

These patients show the catatonic phenomenon of opposition (*Gegenhalten*). Here an attempt to move the body by the examiner evokes an almost equivalent amount of tension in the opposing muscles so that the movement is made difficult. In severe cases this sign is obvious but in milder cases the examiner has to carry out the passive movements rather gently and gradually increase their speed and range in order to recognize the sign. Opposition (*Gegenhalten*) can also be seen in the form of the uplifted head of the psychological pillow. In cases where the illness is very severe any given posture may be maintained for some time (*Haltungsverharren*) but generally this is not very marked and the limbs slowly return to the rest position after the examiner has placed them in an unusual position.

In the author's series two cases were classified as manneristic catatonia and in neither case was there a family history of psychiatric illness.

#### (c) *Proskinetetic Catatonia*

This form was originally called prosectic by Leonhard because of the readiness with which these patients turn towards the examiner when spoken to. However, Leonhard designates this form proskinetic in order to stress the abnormal readiness of these patients to begin automatic movements as a result of external stimuli.

When spoken to these patients turn towards the speaker with an expressionless face which despite its general lack of expression shows a certain degree of interest. The patient may then begin to murmur or further stimulation may cause murmuring. The content of speech is difficult to understand and if it can be made out it is usually a verbigeration of isolated phrases. If the illness is not very marked then the patient may speak in an undertone but it is fairly easy to understand him. In this case sensible replies may be given to questions but many repetitions of the same reply often occur.

Apart from the characteristic speech behaviour these patients have other disorders of motor activity. They have continuous handling movements which

appear when they are spoken to for a short time and when they are examined. They intertwine their fingers, wring their hands, grasp and handle objects, pick and fiddle with their clothes, rub their skin and so on. When the examiner presents his hand they always take it. If they are told that they do not have to take the examiner's hand they do not do so for a short time but after they have been spoken to about something else they will again take his hand when it is offered. They also show co-operation (*Mitmachen*), that is they co-operate fully in all passive movements and help in the movement by contracting the appropriate muscles. Leonhard stresses that the characteristic sign in this illness is *Mitgehen*. By this he means that very light pressure on a part of the body leads to movement in the direction of the pressure. It may thus be possible by very light pressure with one finger to put these patients into very uncomfortable positions. Thus light pressure on the occiput may lead to the patient bending right forwards until his hands touch the floor. Sometimes the patient may finally fall over because the light pressure by the examiner has resulted in an unstable position. When the patient is told not to follow the pressure or to resist it he often does so for a short while but then after some diversionary activity he will again show *Mitgehen*.

These patients can usually occupy themselves when directed but usually show affective flattening with an unconcerned sort of self satisfaction. Excitements are not common in the defect stage and usually then take the form of short attacks of scolding or aggression. In acute stages there are acute excitements when the patient is restless, handles everything, tries to force himself through any open door and attacks other patients.

In the author's series three patients were classified as prosokinetic. In one of these the paternal grandmother had had a mental illness in her sixties with complete recovery. In the other there was no family history of mental illness.

#### (d) *Negativistic Catatonia*

Leonhard's conception of this form does not differ from that of Kleist's (Kleist, 1943, Fish, 1957). He points out however that if the patient is not irritated by the examiner the negativism may show itself mainly as a failure to carry out instructions or to answer questions. If one adopts a friendly approach the patient may show ambivalence. The patient may begin a movement on request then stop or he may begin to answer and then stop. If one examines these patients brusquely and attempts to overcome their negativism by force then severe excitement occurs. These patients show no indications of higher affectivity but their basic drives are preserved. This is seen in their greediness and erotic tendencies. They are liable to make appropriate remarks when least expected.

No patient with this form of catatonia was found in the author's series.

#### (e) *Speech-prompt Catatonia*

This form is the same as that described by Kleist (Kleist, 1943, Fish, 1957). Leonhard stresses the abnormal readiness to speak in the absence of pressure of speech. What apparently is ready at hand in the patient's mind is spoken regardless of its suitability. These patients answer all questions and never tire. If left to themselves they do not speak and sometimes are described as mute in the case notes. In so far as these patients are not stimulated by being spoken to they never appear to bother about their environment.



In the author's series 3 cases were classified as belonging to this group. Only one of these had a family history of mental illness in that an uncle had committed suicide.

(f) *Speech-inactive Catatonia*

Kleist has described this form, but Leonhard's description is more detailed. These patients answer slowly in the early stages of the illness, but later on they usually do not answer at all. When spoken to they look here and there and often make whispering movements with their lips. They become very excited from time to time when they scream and gesticulate in response to hallucinatory voices. In the early stages patients admit to auditory hallucinations of a troublesome kind and also produce fantastic confabulations. However as the illness progresses they become so inaccessible that no evidence can be obtained about these phenomena. All motor reactions as well as speech are slowed down and this is probably due to the patients being distracted by the auditory hallucinations and being unable to attend to stimuli from without. The only initiative, motor activity and affect shown by these patients is in relation to their hallucinations when they are excited.

In the author's series 9 cases were classified as speech-inactive catatonia. Of these only two patients had a family history of psychiatric illness. In one case there was a history of several members of the family having been admitted to mental hospital but details of their illnesses were not available. In another case a niece and the mother had been certified. The illness of the niece resembled that of the patient. The details of the mother's illness were insufficient.

(g) *The clinical pictures of relatives of systematic catatonics*

In cases where a sibling of a systematic catatonic had a schizophrenic psychosis Leonhard found that, where adequate information about the illness was available, it appeared to belong to the same subgroup as that of the proband.

## 2. HEBEPHRENIC FORMS

Leonhard like Kleist considers that affective deterioration is the essential feature of hebephrenia. Apart from this, the illness has an insidious onset with a slowly progressive course and there is no nonsystematic schizophrenia which corresponds with it. In hebephrenia where affective deterioration occurs without marked catatonic or paranoid clinical features there is no resemblance to any nonsystematic form. The hebephrenic forms are poor in symptoms which may lead to diagnostic difficulties especially in mild cases. In the earlier stages nonspecific symptoms may occur and obscure the clinical picture. Depressive and euphoric mood states are common at this stage but states of excitement or inhibition which have a catatonic stamp may also occur. Irritated moods occur early on and often continue into the defect stage.

Leonhard describes four subgroups of hebephrenia which in essentials are the same as Kleist's four subgroups. They are:

- (a) Silly Hebephrenia.
- (b) Eccentric Hebephrenia.
- (c) Shallow Hebephrenia.
- (d) Autistic Hebephrenia.

(a) *Silly Hebephrenia*

These patients have an intense affective blunting which is associated with a contented or mildly cheerful mood. They smile or giggle in a characteristic way and this increases when stimulated by others. There is a marked ethical blunting but owing to their lack of drive they only become criminals in so far as the opportunity presents itself. In the early stages these patients tend to play silly childish tricks on other patients and these tricks are often spiteful and malicious. However, sometimes they become ill-humoured and irritable and then may act spitefully. In the acute stage of the illness mood states of all kinds may occur. As affective blunting progresses these patients lose their drive and hang about in a happy-go-lucky way. They may become so inactive that they give the impression of a catatonic illness but their posture and movements are not catatonic and the silly smiling indicates the diagnosis.

In the author's series two patients were classified as silly hebephrenics, and one of these had a sister who was in the same hospital and was classified as a shallow hebephrenic.

(b) *Eccentric Hebephrenia*

Leonhard stresses the mannerisms and general querulent nature of this illness. It often begins with obsessive compulsive symptoms which Leonhard considers to be precursors of the mannerisms of the defect stage. The mannerisms of these patients are most unlike those of manneristic catatonia as the patient often will not talk about them and tries to keep them secret, so that evidence of their existence comes from the reports of the nursing staff. However the manner of speaking, which is uniform and monotonous, together with repeated querulent complaints and demands, suggests the manneristic quality of the illness. Those patients produce the same grievance time and time again irrespective of the listener's attitude. Thus one has the impression that the patient is not speaking freely but is producing material which has been learned. A mannerism which is very common is that of collecting. These patients often collect rubbish of all kinds. Objects of value may be collected and then the mannerism appears in the guise of senseless stealing. Thus one of Leonhard's patients repeatedly stole bicycles which he could not use.

These patients appear rather cheerless and depressed but the main impression is one of severe affective flattening. In the defect stages no excitements occur despite the querulent attitude but in the earlier stages ill-humoured mood states occur which are associated with irritated excitements. Mood variations do occur in the later stages but are much milder. The affective blunting is associated with an ethical blunting which often leads to antisocial behaviour. These patients often become beggars, tramps and prostitutes. The thinking of these patients appears to be impoverished but performance on intellectual tasks is not too bad and paralogia does not occur.

Leonhard found that in two cases where adequate information about illnesses in the family could be obtained, one proband had a father with a periodic psychosis and the other had a sister with eccentric hebephrenia arrested in a compulsive neurotic state.

Seven cases in the author's series were classified as belonging to this subgroup. Four of these patients had a family history of mental illness. In one case the mother was reported to be insane but no details could be obtained, in another the mother had been an in-patient in a mental hospital



for 25 years before her death and in a third the mother had a mental illness shortly before her death in which there were paranoid ideas and auditory hallucinations. The fourth patient had a mother who for many years had been an in-patient in St. Nicholas Hospital suffering from what at first sight appeared to be a depressive illness. The mother was usually cheerless and never gave any information about herself but she was a trustworthy ward worker and from time to time had agitated depressive moods which responded to a few treatments with E.C.T. It is possible to consider this patient as suffering from eccentric hebephrenia like her daughter.

(c) *Shallow Hebephrenia*

In this form the flattening of affect is very marked. The observer can detect no emotional response when topics which should affect the patient are touched upon. In contrast to this shallow affect these patients are readily accessible and will carry on a reasonable conversation in a factual way. The mood state is one of indifferent satisfaction but it is interrupted from time to time by states of ill-humour when the patient may be anxious, irritated or very rarely euphoric. These unpleasant mood states are associated with hallucinations and ideas of reference; the patient may become extremely excited and aggressive. The hallucinations may occur in all sensory fields but most often they take the form of hallucinatory voices. In spite of the fact that these patients shout at hallucinatory voices when they are excited they have a clear understanding of the morbid nature of these voices when the excitement dies away. Leonhard suggests that these hallucinatory voices are of the nature of pseudo-hallucinations. There is a general lack of initiative but these patients will take part in the day to day activity of the mental hospital and do not have to be closely supervised. Leonhard could obtain adequate information about a psychiatric illness of a relative in only one case; here the patient had a brother with shallow hebephrenia.

In the author's series two patients were classified as shallow hebephrenia and one of these had a sister with silly hebephrenia.

(d) *Autistic Hebephrenia*

In this form there is a combination of autism with marked affective blunting. The facial expression is stiff and impenetrable and as in speech-prompt catatonia the observer can guess nothing about the patient's inner life from his facial expression. States of ill humour occur in which the patient is very irritated and shouts threats or accusations at someone in the environment. These may be followed by attacks on the selected person. Thus these states differ from those in shallow hebephrenia in that the aggression is directed against a specific person. On the whole the mood is one of rejection mixed with discontent and is reminiscent of the mood of the eccentric hebephrenic. Thus it is in contrast with the indifferent satisfaction of the silly and shallow hebephrenics. Usually the patients give short off-putting answers to intelligence questions but where they do answer it seems that the defect in intelligence is not very great. Initiative is of course deficient but these patients can frequently be trained to do a job requiring some independence of action. They carry out such jobs efficiently but if they have to speak they only say the absolute minimum required. They tend to avoid others and walk past people whom they know without speaking.

Only one autistic hebephrenic patient of Leonhard's had a relative with

a psychiatric illness where the clinical details were available. In this case an aunt of the proband had a combined form in which one of the components was autistic.

In the author's series five cases were classified as autistic hebephrenics and not one had a family history of mental illness.

(e) *Clinical pictures of relatives of systematic hebephrenia*

In most cases of systematic hebephrenia with a family history of mental illness Leonhard could not obtain adequate information. Where such information was available the same sort of illness as that of the patient was found.

### 3. PARANOID FORMS

In common with many German authors Leonhard uses the term paraphrenia to designate all the paranoid schizophrenias. These illnesses are of course characterized by delusional ideas and sense deceptions but thought disorder is also present and plays a role in the production of paranoid symptoms. Leonhard believes that the disorder of the logical progress of thought is a prerequisite for the setting free of some of the contents of the patient's own thinking which are then able to appear independently as hallucinations. However, delusional ideas in paranoid schizophrenia are also connected with the thought disorder. Leonhard does not separate off from the other paranoid schizophrenias a group of confused schizophrenias, where thought disorder is the leading symptom. He points out that the more severe the thought disorder is the more severe are the paranoid symptoms. So that in incoherent paraphrenia one finds the most severe degree of thought disorder associated with the most severe variety of hallucinations.

As in the other systematic schizophrenias accessory symptoms in the acute stage of the systematic paraphrenias make accurate diagnosis difficult. Anxiety and other affective disorders may occur, perplexity is not uncommon and ideas of reference also appear. These symptoms may mask the specific symptoms which as a rule are already present. If one is familiar with the essential symptoms because of an acquaintance with advanced cases then it is often possible to find them in the acute syndrome. It is rather rare to find any other symptoms but paranoid ones. Catatonic symptoms are only very rarely present at some stage of the illness. Symptoms suggesting hebephrenia are also scarcely ever present. Severe affective disorders are unusual in systematic paraphrenias, and suggest affect-laden paraphrenia. Acute onset is more in favour of a nonsystematic schizophrenia; often systematic paraphrenias run an insidious course.

In his descriptions of systematic paraphrenias, Leonhard is more precise than Kleist. He insists that the subforms are precise syndromes and he describes the symptoms in detail. The present author found that it was particularly in the paranoid forms that Leonhard's views and descriptions were superior to those of Kleist.

Leonhard has described six subforms of systematic paranoid schizophrenia. These are:

- (a) Hypochondriacal Paraphrenia.
- (b) Phonemic Paraphrenia.
- (c) Incoherent Paraphrenia.
- (d) Fantastic Paraphrenia.
- (e) Confabulatory Paraphrenia.
- (f) Expansive Paraphrenia.



(a) *Hypochondriacal Paraphrenia*

This corresponds to Kleist's progressive hallucinatory somatopsychosis (Kleist, 1949, Fish, 1957a), but unlike Kleist, Leonhard considers that specific bodily hallucinations, specific hallucinatory voices and a certain mood state must all occur for this subform to be diagnosed.

The bodily hallucinations are usually referred to internal organs and are usually described so grotesquely that it is impossible for a normal person to empathize with the patient. Often these sensations can only be described in a general way such as "tortures", "misuse" and so on. The patient may produce technical neologisms in order to designate these sensations. Hallucinations of smell and taste may occur but are not characteristic. Visual hallucinations occasionally are present in the early stages when the patients see frightening visions but later in the illness they are not prominent and an abundance of visual hallucinations would be against the diagnosis of hypochondriacal paraphrenia. Hallucinatory voices (phonemes) consist of short phrases which are only partly connected with what the patient is thinking and do not fit in with his thoughts like the phonemes in phonemic paraphrenia. In the early stages the phonemes often have a close connection with the patient's thought, and *Gedankenlautwerden* can even occur. In the later stages the phonemes are usually disconnected phrases, especially insulting words, without any real sense so that the patient usually is unable to remember and reproduce them. The patient is distressed by the occurrence of the voices as such and not so much by their content. The voices and sensations are usually attributed to apparatuses which affect the patient from a distance but more rarely they are attributed to people in the environment.

These patients have a permanent morose dissatisfied mood which can often develop into irritation. They are often querulent and complain bitterly about their hallucinations. If one contradicts their assertions they easily become excited. They frequently insist on their discharge in a monotonous way. Thus their affectivity is well preserved and their interest in their home and family never flags.

These patients have thought disorder. They tend to wander from the point, talk about subjects loosely related to the task in hand and are inclined to verbal derailments. Leonhard calls this unconcentrated thinking.

Leonhard could only obtain sufficient information about mental illness in the family of one patient with hypochondriacal paraphrenia. In this case the brother had a combined illness and hypochondriacal paraphrenia was one component of this.

In the author's series seven cases were classified as hypochondriacal paraphrenia. In two of these there was a family history of mental illness. One had a maternal uncle who died in a mental hospital and the other had an aunt and a great aunt who died in mental hospitals. No information about these relatives was available.

(b) *Phonemic Paraphrenia*

Leonhard has also designated this subform as verbal hallucinatory paraphrenia and considers it to be the mildest subform of systematic schizophrenia. The outstanding symptoms are the hallucinatory voices which Leonhard calls phonemes; a use of the word which in English is not in keeping

with accepted definitions.\* Bodily hallucinations and hallucinations of smell and taste do not occur. The hallucinatory voices are quite different in quality from those of hypochondriacal paraphrenia. They are closely related to the patient's thinking and the patient treats them as real people with whom it is possible to hold a conversation. The voices often contradict or confirm what the patient is thinking. The hypochondriacal patients are never seen talking to their voices but merely complain about the voices as such, whereas the phonemic paraphrenics are upset by the content of the voices. *Gedankenlautwerden* occurs and not only are the thoughts spoken aloud as the patient thinks but they may also be spoken to the world at large so that the whole world knows what the patient thinks. The content of the voices is also affect-laden not in the sense of abusive words as in hypochondriacal hebephrenia but in the sense that the voices talk about those things which are unpleasant and disturbing to the patient. The voices are rarely attributed to apparatuses but often are thought to come from the wireless or to be due to people in the environment, who may be close to the patient or some way away. They may also be attributed to invisible beings such as spirits or witches. Sometimes the voices emerge from within the body. Thus one of the author's patients had three voices coming from her chest due to the Crown Prince of Germany and two staff nurses being inside her chest. Visual hallucinations occasionally occur but are never important. The mood state of these patients is usually well balanced, but when they talk about the unpleasant things the voices say they may become angry. In the later stages however they become resigned to the trouble and talk about the voices calmly whereas the hypochondriacal paraphrenics never become habituated to their hallucinations and continue to complain bitterly about them even in the late stages. The affective responsiveness of the phonemic paraphrenic is well preserved so that they are usually parole patients and carry out responsible jobs in institutions. Many of them never need hospital admission. One can of course talk of an affective blunting since these patients finally tolerate their unpleasant symptoms rather patiently.

In general conversation these patients show little disorder of thinking but in problem solving they are unable to orientate themselves towards an objective of thought and talk about the problem indecisively. In simple problems they are often successful. Leonhard calls this disorder woolly thinking.

Leonhard had four patients with family histories of mental illness, but could only obtain sufficient information in two cases. In one case a patient had an uncle with phonemic paraphrenia and in the other the patient had an aunt with combined fantastic phonemic paraphrenia.

In the author's series there were twelve cases classified as phonemic paraphrenia. In four cases there was a family history of mental illness. In one case the mother had committed suicide and in another the paternal great-grandmother was in a mental hospital for some years and died there, but no information about her illness was available. One patient had a brother who committed suicide and a mother who was in St. Nicholas Hospital from the age of 70 to 93 when she died with delusions of persecution and auditory hallucinations in the presence of complete disorientation for time and place. This illness was possibly a combined hypochondriacal and phonemic paraphrenia released by senile deterioration. The fourth patient had an aunt and

\* The *Shorter Oxford English Dictionary*, 1955, defines phonemes as "A speech sound considered in respect of its functional relations in a linguistic system". In this article it will be used in Leonhard's sense of an hallucinatory voice.



a maternal grandmother who were in mental hospitals for many years and died there. No details were available about the grandmother's illness but the aunt appeared to have had hypochondriacal hallucinations and phonemes but an adequate account of the phonemes was not available.

### (c) *Incoherent Paraphrenia*

In this subform the auditory hallucinations are prominent even in the early stages but thought disorder only becomes marked when the hallucinations become very severe. In the early stages bodily hallucinations are commonly reported but later they are not present. Occasionally one can separate out confabulatory remarks from among the incoherent expressions in these patients and Leonhard supposes that these are probably derived from visual hallucinations. In the later stages the patients are entirely occupied by their auditory hallucinations. The facial expression shows that they are not turning towards the examiner but that their attention is directed entirely towards their inner experiences. The patient may look here and there and not look at the examiner very much or he may look at the examiner with a peculiar rigid gaze. The patient hallucinates in conversation and can often be seen whispering or talking quietly to the voices. Now and then they become excited and talk loudly and shout abuse at their voices often denying insults or accusations; shouting out for example, "You're a liar", "You rotten swine", etc. The hallucinatory aversion, and the continuous hallucinosis which cuts into all conversations, occur in no other form of paraphrenia. These patients show no initiative and have no interest in anything. When asked questions their replies are short and perfunctory and are often given in a very low voice. Their utterances show that they have a very severe thought disorder in which incoherence is associated with contaminations.

In one case with a family history where adequate information was available Leonhard was able to deduce that the great niece of the patient had incoherent paraphrenia.

In the author's series ten cases were classified as incoherent paraphrenia. Five of these patients had a positive family history. In two cases an uncle was reported as insane but no information was available. In one case an aunt had been in a mental hospital and in another the mother had committed suicide. In one case the brother had been in St. Nicholas Hospital from February 8th, 1934, to November 18th, 1935, when he had auditory hallucinations, believed he was unclean and at times was violent and put his head through windows. A note one year after admission reads, "Brain is nullified. Hears voices of other patients at night".

### (d) *Fantastic Paraphrenia*

Leonhard regards this as a paraphrenic illness in which hallucinations and delusions play an equal part. Bodily hallucinations are always marked and are always described in a grotesque way which makes it impossible for the examiner to empathize with the patient. Leonhard says that the description of the bodily sensations resembles that of the hypochondriacal paraphrenia, but this is the only symptom which is apparently qualitatively the same in two different subforms of systematic schizophrenia. Hallucinatory voices are less obtrusive but visual sense deceptions play an important role in this subform. Isolated visions may be seen but the characteristic symptom is the scenic hallucination in which scenes are visualized and accompanied

by auditory and somatopsychic experiences. Often these are scenes of horrible tortures and mass murders. This phenomenon partly accounts for the fantastic quality of the illness. However this fantastic element is strengthened by the manifestly absurd ideas which these patients have in which they treat everyday practical experiences with indifference. The same sort of manifest illogicality also occurs in the misidentification of people in the environment when the patient regards such people as being quite different personalities with a preference for the highly placed. The grandiose ideas which these patients have are also absurd. They elevate themselves to an extraordinary degree and often call themselves God, but they draw no conclusions from these grandiose delusions and do not object to being treated as patients.

Their affect is shallow and if their ideas are laughed at they may flare up somewhat but the affect quickly dies away. However they often maintain a definite interest in their environment and are usually interested in their family. Superficially their general attitude often appears to be quite natural. When they talk about their fantastic ideas they frequently become somewhat muddled but if one questions them carefully then the train of thought becomes fairly clear. Leonhard considers that with intelligence questions one can show that the main feature of thought disorder in this subform is derailment.

Only one case of Leonhard's was considered to have a positive family history of mental illness and insufficient information was available about the relative's illness.

In the author's series nine cases were considered to have fantastic paraphrenia and of these two had family histories of nervous illness. In one case the mother was described as neurotic and in the other the brother had a mental illness which caused him to be admitted to an observation ward under Section 20 of the English Lunacy Act. In both these relatives no further details were available.

#### (e) *Confabulatory Paraphrenia*

In this form the outstanding feature is the presence of falsifications of memory which are produced as well-organized descriptions of past experiences. In some cases in the early stages there may be dream-like experiences which appear to be the precursors of the later confabulations but in other cases confabulations may clearly be present at the onset. The characteristic confabulations generally have a fantastic quality and are concerned with other parts of the world, other worlds or even the moon and stars. The patient's confabulations are plastic and detailed descriptions of the alleged events are given. Leonhard suggests that in these patients, images which emerge spontaneously, acquire a sensory character which normally is only associated with memories. As the patients correctly evaluate their immediate environment, Leonhard presumes that critical sense will only allow the confabulations to be valid when they are concerned with other places and other times. Quite a number of these patients account for their fantastic experiences by saying that they happened in dream states or trance states and so on. Leonhard regards this as an indication of partial preservation of the patient's critical sense. These patients also have what Leonhard has called "perceptual falsifications" in which objects in their environment, especially people, continually appear to be different. Thus the size, shape and general appearance



of things change from day to day. Leonhard explains this as an abnormally detailed concretization of presentations so that for example when a person is seen by the patient he is contrasted with the detailed memory image of his appearance the day before and the different features of his present appearance are emphasized, while the general similarity is overlooked. Grandiose ideas which are often very extravagant also occur and are always worked into the confabulations. The patients have an elevated mood which supports the grandiose delusions and partly contributes to the fantastic and sensational character of the confabulations.

Leonhard considers that the thought disorder in this subform enhances the fantastic and sensational nature of the confabulations because in the thinking of these patients transition from concrete to abstract thought is disturbed so that while these patients can maintain a critical judgment in concrete thinking they cannot carry out abstract tasks. Thus in everyday life they are well ordered but in intelligence tests they show a peculiar pictorial form of thinking.

In two cases with a family history of psychosis Leonhard could not obtain sufficient information about the illnesses of the relatives to classify them.

In the author's series three cases were classified as confabulatory paraphrenia. One of these patients had a mother who had died in a mental hospital but no information about her illness was available.

#### (f) *Expansive Paraphrenia*

This is a form of paraphrenia which in the later stages is purely delusional. In the early stages sense deceptions occur but later they are absent and thus this subform is quite unlike any other systematic paraphrenia. The delusions are always expansive and are not associated with persecutory delusions. However the grandiose ideas are within reasonable limits and the patient acts according to his grandiose ideas. In the fantastic and confabulatory paraphrenias the grandiose delusions do not lead to any expansive behaviour, but in expansive paraphrenia the patients behave as if they were highly placed so that the whole personality is much more affected by the grandiose delusion. They adopt a kind of haughty pose and take on a superior attitude when dealing with others; thus they are familiar in a friendly way with the doctors and tend to look down on their fellow patients. They tend to try to impress by their style of dress, the use of high-sounding phrases and the production of secret documents which are written in code. Usually the expansive behaviour and productions of these patients have a very monotonous character as the same ideas and attitudes are repeated without much variation. This is in contrast to the richness of ideas of the confabulatory and fantastic paraphrenics. The expansive paraphrenics tend to become garrulous when they speak about their grandiose delusions and they bring forward their requests and complaints with a great deal of verbosity. They carry out their expansive behaviour and activities with a certain amount of eagerness but otherwise there is a general deficiency of initiative. The affect of these patients gradually becomes blunted and in the final stage they do not become irritated even if laughed at.

These patients have a very marked thought disorder which mainly affects the verbal side of thinking so that they frequently make mistakes in grammar and word formation. Leonhard is of the opinion that concepts are not absent in these patients but they are very inexact and the finer details of the concepts

are missing. In view of this he designates the thought disorder as a coarsening of thinking.

Leonhard had three patients with a family history of mental illness but in only one of these cases was there adequate information about the relative's illness. In this case the father of the patient appeared also to have suffered from an expansive paraphrenia.

In the author's series no case was classified as expansive paraphrenia.

(g) *The clinical pictures of relatives of patients suffering from systematic paraphrenia*

In Leonhard's cases it was only possible to obtain adequate information about the illnesses of relatives in a few cases. In all these cases except one, the relative appeared to have had the same subform of paraphrenia either on its own or combined with another subform. Leonhard concludes that these facts support his view of these subforms as independent genetic entities.

### E. COMBINED SYSTEMATIC SCHIZOPHRENIAS

Leonhard considers that combinations of different systematic schizophrenias may occur. The clinical pictures are then as definite as in the simple subforms but they do not necessarily consist of a simple addition of the symptoms of the two clinical pictures because the two different syndromes may influence each other in a reciprocal way. Up until now Leonhard has only definitely found such combinations within the major groups of systematic schizophrenia, *i.e.*, catatonia, hebephrenia and paraphrenia and he has not had to postulate such combinations as catatonic-hebephrenic, catatonic-paraphrenic or hebephrenic-paraphrenic.

In the combined forms the diagnosis can only be made in the defect states since in the early stages the accessory symptoms are much more marked than in the simple forms.

In the descriptions of combined forms which follow only a rough idea of Leonhard's views can be given. In some cases the combined form has been found fairly frequently while in others only one possible case has been found. In the latter case the characteristics of the combined form can only be provisionally accepted and it is hoped that in further investigations the clinical details of such a combined form will be more clearly established. The combined forms will be presented in the following way. The five combinations of one form with the other forms, then the four combinations of another form with the remaining four other forms and so on. This method of presentation has been carried out in order to present the matter in an orderly way. It must not be concluded that the designation of a combined form, for example, as speech-prompt negativistic catatonia means that the speech-prompt component is any more important than the negativistic.

#### 1. COMBINED SYSTEMATIC CATATONIA

##### (a) *Combinations of Speech-prompt Catatonia*

Leonhard has found combinations of speech-prompt catatonia with all other varieties of catatonia. The clinical pictures of these combinations will now be briefly outlined.

##### (i) *Parakinetic speech-prompt catatonia*

*Vorbeireden* is present but the frequent repetition of words suggests perseveration. The senselessness of the answers and the tendency to neo-



logisms are no more pronounced than in simple speech-prompt catatonia. There is however a tendency to answer briefly and to develop pressure of speech as the questioning proceeds. This is a modification of the speech-prompt element by the parakinetic.

In the motor sphere there is marked parakinetic overactivity but it tends to be more uniform than the parakinesia of the simple parakinetic and frank iteration may occur at times.

Thus one may say that the parakinetic over-activity is modified in the direction of uniformity and the readiness to speak develops into a pressure of speech. So that each constituent illness modifies the other.

(ii) *Manneristic speech-prompt catatonia*

There is a definite rigidity of the mimicry and posture which is characteristic of manneristic catatonia. There is a characteristic modification of the *Vorbeireden* in that the mild uniformity which occurs in speech-prompt *Vorbeireden* is increased to such an extent that marked verbal stereotypy and perseveration occur. Some factual answers are produced now and then.

These patients also show a marked auditory hallucinosis which scarcely ever occurs in manneristic catatonia.

(iii) *Proskinetetic speech-prompt catatonia*

These patients show the typical proskinetetic attitude of coming towards the examiner. Forced grasping and *Mitgehen* occur in association with intertwining movements of the hands and murmuring. When spoken to, these patients reply readily with senseless answers containing neologisms and agrammatical repetitions, which are characteristic of the speech-prompt. The proskinetetic patient gives a simple sensible reply when he does answer a question and the speech-prompt patient's answers are not entirely senseless. The utter senselessness of the answers of the combined patients can be understood as an increase in the speech impulse due to the proskinetetic element.

(iv) *Negativistic speech-prompt catatonia*

The *Vorbeireden* is clearer than in combination with manneristic catatonia but is more uniform than in the typical speech-prompt. The patients frequently show their negativism by saying "I don't know" in reply to questions. The patients sit in a cramped bent forward position, twisted away from the examiner but look in the examiner's direction from time to time. Leonhard had two cases of this combination and in one case the patient drew back and became hostile when the examiner tried to grasp the patient's hand, but in the other the negativism was milder and there was a tendency to ambtendency.

Both patients had typical negativistic excitements in which they threatened people in their environment. They also had marked auditory hallucinosis which seldom occurs in simple negativistic catatonia whereas, of course, excited states occur in speech-prompt catatonia which are partly or wholly conditioned by auditory hallucinations.

(v) *Speech-inactive speech-prompt catatonia*

Since Leonhard postulated that as these two forms of catatonia were due to affections of antagonistic members of a paired system, then the combination would not be expected to be a simple addition of the symptoms of the two forms. In four cases he considered that a combination of speech-inactive and speech-prompt catatonia was present. In one case *Vorbeireden* was no longer detectable but there was slight indications of it at times. The tendency to reply was present and this was marked in the other three cases

It appeared as if the speech-inactive component diminished the motor impulse and made the *Vorbeireden* more uniform. In one case verbal stereotypies and perseveration were very prominent. At times a verbigeratory repetition of the same expression occurred in these patients so that individual words or phrases were repeated two or three times. A tendency to reply with meaningless incomplete answers replaced the *Vorbeireden*. This can be considered as related to the tendency to talk at random which occurs in speech-prompt catatonia.

Inactivity of speech did not occur but the continuous auditory hallucinosis of the speech inactivity was always present. Whilst being spoken to these patients turned away now and then towards one side or the other and spoke to their voices. The other feature due to speech-inactive catatonia was the presence of fantastic confabulatory ideas. These are present at the onset of speech-inactive catatonia and are not produced in the defect stages owing to poverty of verbal expression. Any combination with a form of catatonia which increases the speech impulse will bring about the expression of the fantastic confabulatory ideas.

## (b) *Combinations of Speech-inactive Catatonia*

### (i) *Parakinetic speech-inactive catatonia*

The parakinetic overactivity is the same as in the simple form. Speech is parakinetically distorted, it appears in jerks, is chopped up and contains stereotyped expressions. Fantastic confabulations occur. The characteristic hallucinatory aversion of the speech-inactive is present. In conversation it is often difficult to decide whether a remark is meant for the examiner or the hallucinatory voices. Severe hallucinatory excitements occur as in speech-inactive catatonics and are accompanied by marked parakinesia. The abruptly changing thought of the parakinetic is combined with the incoherence of the speech-inactive so that a marked changeability of thought occurs and the theme is never maintained. The parakinesia is more uniform and contains more clear parakinetic mannerisms than in the simple form.

### (ii) *Manneristic speech-inactive catatonia*

Leonhard has found no clear case of this combination.

### (iii) *Proskinetetic speech-inactive catatonia*

The typical proskinetetic signs occur together with fantastic confabulations of a disordered kind. Severe thought disorder occurs. Words and sentences are frequently repeated so that verbigeration often occurs. The effects of the proskinetetic component can be seen in all these phenomena. The speech-inactive component also shows itself in hallucinatory aversion. The patients turn away and whisper with the voices.

### (iv) *Negativistic speech-inactive catatonia*

Not a word is said by these patients when they are spoken to. The negativistic behaviour is less obvious than in the simple form. They are not as cramped and twisted sideways as the simple negativistics, but appear more to be sunk into themselves. They tend to look away from the examiner. Continuous hallucinosis is not obvious probably because of the negativistic component. Nevertheless clear hallucinatory excitements, like those in speech-inactive catatonia, do occur as well as negativistic excitements.



(c) *Combinations of Negativistic Catatonia*(i) *Parakinetic-negativistic catatonia*

These patients show a general negativistic attitude together with typical parakinetic overactivity. *Vorbeireden* of a negativistic kind occurs. Whereas in speech-prompt catatonia that which lies to hand is immediately spoken, here the talking past the point appears to be a deliberate refusal to give the right answer. Sudden changes in thought also occur in this combination.

(ii) *Manneristic-negativistic catatonia*

Leonhard postulated this combination in one case where the patient gave no answers to questions, resisted all interference but carried out a mannerism of kissing the ground very quickly. She also showed an embarrassed giggling. Leonhard had some doubt about this case owing to the speed with which the mannerism was carried out, but he points out that negativistic catatonics can act very quickly when they steal food or run away from the nursing staff.

(iii) *Proskinetic-negativistic catatonia*

Leonhard has postulated this combination in one case. In this patient murmuring was absent but interlacing movements of the hands were present. Sometime the patient showed the attitude of coming towards the examiner but at other times there was negativism. The posture and mimicry was mainly that which is found in negativistic catatonia.

(d) *Combinations of Proskinetic Catatonia*(i) *Parakinetic-proskinetic catatonia*

Parakinetic activity is present but tends to become manneristic. Leonhard suggests that this uniformity of the parakinesia is due to the automatic nature of the proskinetic activity. Clear verbigeration occurs and this can be seen as an accentuation of the murmured verbigeration of the proskinetic.

(ii) *Manneristic-proskinetic catatonia*

Here the stiff rigid mimicry of the manneristic is combined with the proskinetic activity. The intertwining of the fingers and the fingering of clothes tends to become stereotyped.

(e) *Parakinetic-manneristic catatonia*

The parakinetic activity is carried out slowly and is made very uniform by the manneristic component. The facies and the attitude of the body are rigid. The course of the parakinetic movements is slow. The parakinesia occurs on stimulation but without stimulation the patient remains fixed for a long time in a rigid posture.

(f) *Combined Forms in the Author's Series*

In the author's series six cases were classified as combined catatonias.

In one case a combination of manneristic and proskinetic catatonia was present. This patient had an uncle who had been in a mental hospital and two sisters who were mental defectives.

Two patients were classified as manneristic-speech prompt catatonics. One of these had a father who died in a mental observation ward and a paternal aunt who died in a mental hospital. Unfortunately, no further information was available about these relatives.

Three patients were considered to have proskinetic-speech inactive catatonia. No family history was obtained in these cases.

## 2. COMBINED SYSTEMATIC HEBEPHRENIAS

Leonhard has found all possible combinations of systematic hebephrenias.

### (a) *Combinations of Silly Hebephrenia*

#### (i) *Eccentric-silly hebephrenia*

These patients show the querulent monotonous complaining of the eccentric hebephrenic but the smiling or giggling of the silly hebephrenic is also present.

#### (ii) *Shallow-silly hebephrenia*

One patient observed by Leonhard showed the typical smiling and behaviour of the silly hebephrenic but also had a complete absence of emotional response when normal affect-laden themes were discussed. Violent ill-humoured states similar to those of shallow hebephrenia also occurred.

#### (iii) *Autistic-silly hebephrenia*

Leonhard had one case in which he postulated the presence of this combination. This patient cut himself off from all contact and was irritable and tense at times. When an effort was made to get into contact with him he often smiled and laughed for no reason.

### (b) *Combinations of Eccentric Hebephrenia*

#### (i) *Shallow eccentric hebephrenia*

The emptiness of affective expression is much greater than in the eccentric form. There is a marked poverty of drive so that the monotonous querulent complaints are less prominent than in the eccentric. They have to be encouraged to talk, otherwise they sit about doing nothing and do not participate in any activities. The querulent complaining and the repeated use of a few phrases and expressions with slight modifications indicates the eccentric element. Periodic ill-humoured states like those in shallow hebephrenia also occur.

#### (ii) *Autistic eccentric hebephrenia*

The autistic attitude is well marked but when spoken to the patient becomes querulent and brings forward his complaints in a rather fixed way. Excitements like those in autistic hebephrenia also occur.

### (c) *Combinations of Shallow and Autistic Hebephrenia*

Apart from the combinations mentioned above, combinations of shallow and autistic hebephrenias are found. The autistic attitude is present but it is associated with a severe devastation of affect. Affect-laden themes produce no more response than indifferent ones. Speech is freer than in autistic hebephrenia and the response to questions is better. Ill-humoured states occur in which there may be marked violence.

### (d) *Combined forms in the Author's series*

Two patients in the author's series were classified as silly eccentric hebephrenia and one as silly shallow hebephrenia. There was no family history of mental illness in the silly shallow hebephrenic but one silly eccentric hebephrenic had an aunt who died in a mental hospital and the other had a paternal aunt and uncle who were reported to have been "queer". Further details of the illnesses of these relatives were not available.



### 3. COMBINED SYSTEMATIC PARAPHRENIAS

Leonhard points out that the combined paraphrenias produce more complicated clinical pictures than the combined catatonias and hebephrenias. Sometimes a simple summation of symptoms occurs but often the symptoms influence one another or new unexpected symptoms emerge.

#### (a) *Combinations of Hypochondriacal Paraphrenia*

##### (i) *Phonemic hypochondriacal paraphrenia*

Typical bodily hallucinations occur, but hallucinatory voices are more prominent than in either simple form and the patient hallucinates during conversation. Thought disorder is severe and there is a peculiar inability to fix on the topic under discussion. Patients tend to pass into general expressions so that it may be impossible to get a factual answer.

##### (ii) *Incoherent hypochondriacal paraphrenia*

The patient speaks in fragmented phrases made up of a few words, the meaning of which is far from clear. The patient answers questions and speaks to his voices at the same time. Bodily hallucinations of a fantastic kind occur and hallucinatory excitements when the patient shouts at his voices.

##### (iii) *Fantastic hypochondriacal paraphrenia*

The bodily sensations which occur in both forms are much more pronounced in the combined form, and they acquire a fantastic colouring. Thus one patient no longer had a brain and another had no diaphragm. Misidentifications, hallucinations, in all spheres, massive visual hallucinations and absurd fantastic ideas occur. Apart from the increased severity of the bodily hallucinations the combined form differs from its components in the severity of the thought disorder. These patients are severely muddled even when discussing indifferent topics and pressure of speech is common. The muddledness is so severe that it is reminiscent of Kraepelinian schizophasia.

##### (iv) *Confabulatory hypochondriacal paraphrenia*

The somatopsychic and confabulatory phenomena occur side by side in this combined form. Bodily sensations are partly elaborated in a confabulatory way. Voices typical of the hypochondriacal component occur. Visual experiences occur and this indicates the confabulatory component. There is poverty of drive and these patients do not say much on their own accord. When spoken to they respond but soon revert to their inactive attitude. This appears to be a new system produced by the combination.

##### (v) *Expansive hypochondriacal paraphrenia*

Grandiose ideas and the external pose of superiority occur together with an eccentric manner of speaking and the use of peculiar words. Pressure of speech occurs and this is probably due to the hypochondriacal component as is the increase in the expansive talkativeness which may also occur. If questioned cautiously these patients will talk about their auditory and bodily hallucinations.

#### (b) *Combinations of Phonemic Paraphrenia*

##### (i) *Incoherent phonemic paraphrenia*

The incoherent component dominates the picture and the patient talks to his hallucinatory voices in the presence of the examiner. Answers to questions are usually incoherent but the patient manages to fix on to the topic better

than the simple incoherent. The thought disorder is less marked than in simple incoherent paraphrenia. This fact together with the continuous auditory hallucinosis leads Leonhard to postulate a phonemic component.

(ii) *Fantastic phonemic paraphrenia*

The muddledness is much greater than in simple fantastic paraphrenia but the usual fantastic features such as absurd ideas, misidentifications and expansiveness occurs. Hallucinatory voices are very marked but bodily hallucinations are less prominent than in simple fantastic paraphrenia.

(iii) *Confabulatory phonemic paraphrenia*

Hallucinatory voices occur and fit into the content of the patient's thought. Confabulations occur as such or as visual hallucinations. The train of thought is not disturbed very much.

(iv) *Expansive phonemic paraphrenia*

The typical expansive behaviour occurs in association with verbal hallucinosis. General activity is somewhat increased. These patients are more active and more interested in their surroundings than the simple expansives.

(c) *Combinations of Incoherent Paraphrenia*

(i) *Fantastic incoherent paraphrenia*

In these patients fantastic material is produced but it is disconnected and fragmented. The patient talks continually with his voices in the presence of the examiner.

(ii) *Confabulatory incoherent paraphrenia*

In these patients clear confabulations are present but speech consists of the fragmented utterances typical of incoherent paraphrenia. The thought disorder is not so severe as in simple incoherent paraphrenia and in intelligence questions the patients do not wander too far from the topic under discussion.

(iii) *Expansive incoherent paraphrenia*

In these patients there is a haughty pose and grandiose ideas occur, but the train of thought is fragmented. Individual phrases are expressed one after another without any connection and separated by short pauses. Hallucinatory voices occur as in incoherent paraphrenia and their presence can be deduced from the hallucinatory excitements, and from the disjointed speech.

(d) *Combinations of Fantastic paraphrenia*

(i) *Confabulatory fantastic paraphrenia*

The typical fantastic clinical picture is seen, but well-organized confabulations are also present. There is a marked muddled state and pressure of speech. The presence of confabulations despite the severe muddledness indicates the confabulatory component.

(ii) *Expressive fantastic paraphrenia*

In these patients the expansive component shows itself in the haughty attitude, the affected manner of speaking and the use of peculiar words. In addition the typical fantasia is present. Thought disorder is more severe than in either simple form.

(e) *Combinations of confabulatory and expansive paraphrenia*

Apart from the confabulatory expansive combination all other possible combinations of these forms have been described above. In the confabulatory



expansive form, confabulations occur but they may occur in transitional forms like visual hallucinations. The confabulations tend to be more uniform and less plastic than in the simple form and this may be due to the expansive component since uniformity is usually present in the thinking of the expansive. The typical expansive symptoms also occur.

(f) *Combined paraphrenias in the author's series*

Three cases in the author's series were classified as combined fantastic phonemic paraphrenia. One of these patients had a family history of mental illness; her uncle was reported as having suffered from "religious mania".

One case was classified as phonemic confabulatory paraphrenia and had no family history of mental illness.

Three cases were classified as fantastic incoherent paraphrenias and in none of these was there a family history of mental illness.

F. DIFFERENCES IN RECLASSIFICATION

If Table 1 is compared with the results previously published by the author (Fish, 1958) certain discrepancies will be noted. It is now necessary to discuss the extent and significance of the differences in classification of the original series when classified according to Kleist and according to Leonhard.

Forty-one cases were originally classified as atypical, simple or combined systematic paranoid schizophrenia and 5 cases as combined paranoid and confused schizophrenia. Of 7 cases classified as progressive reference psychosis 4 have been reclassified as non-systematic schizophrenias; 22 as affect-laden paraphrenia and 2 as schizophasia. As Kleist's progressive reference psychosis probably includes some schizophasics in Leonhard's sense (Kleist, 1949) then these last two cases were not substantially misclassified. The other three cases were classified as phonemic paraphrenia, incoherent fantastic paraphrenia and eccentric hebephrenia. Nineteen systematic paraphrenias were reclassified in groups consistent with Kleist's groups but 15 were classified into different groups. Of these 4 were originally classified as combined forms but were reclassified as a simple form which corresponded to one of the components of the combined form. Three cases were reclassified as combined forms and one component was similar to a component of the original combination. Thus 7 cases were only partly reclassified. Of the 8 other cases 1 was reclassified as catatonia, 2 as affect-laden paraphrenia and 5 as simple systematic forms. Of the 5 cases classified as combined paranoid and confused schizophrenias 1 was reclassified as a catatonic. Two cases which were originally classified as fantastic incoherent schizophrenias were reclassified as incoherent paraphrenia and fantastic incoherent paraphrenia. One case classified as incoherent schizophrenia combined with progressive autopsychosis was reclassified as incoherent schizophrenia and one case of fantastic paralogical schizophrenia as fantastic paraphrenia. To sum up, of the 46 cases, 34 were reclassified in a Leonhard subgroup substantially the same as the original Kleistian subgroup. 9 cases were reclassified into different paranoid subgroups and 3 into non-paranoid subgroups.

Among the 18 catatonias of the original series the two unclassified catatonias have been reclassified as nonsystematic schizophrenics, one as a periodic catatonia, the other as a schizophasia. Two cases classified as atypical (iterative) catatonia have been reclassified as manneristic speech-prompt

catatonia. Six cases were reclassified into a group similar to the original Kleistian group and 6 into different subgroups of systematic catatonia; 5 as different simple systematic catatonias and 1 as a combined systematic catatonia. 2 cases were reclassified as non-catatonic illness. Thus only 6 out of the original 16 classified catatonics were reclassified in a group substantially the same as the original Kleistian group.

As Leonhard does not recognize a confused group of schizophrenias, then all those cases classified as schizophasia (including atypical, shifting, confused schizophasia), or incoherent schizophrenia must be considered to be classified in substantially the same groups as they originally were if they are reclassified as schizophasia or incoherent paraphrenia respectively. Two cases classified as schizophasia were reclassified as schizophasia in Leonhard's sense and 3 cases classified as atypical shifting confused schizophrenia were reclassified as schizophasia. One case classified as atypical shifting confused schizophrenia was reclassified as periodic catatonia. In view of the differences between Leonhard's and Kleist's schemes of classification, these 6 cases can be considered as being reclassified in substantially the same group as before. Two cases of schizophasia were reclassified as hebephrenia and catatonia respectively, and one atypical confused shifting schizophrenia was reclassified as a systematic catatonia. Four incoherent schizophrenias were reclassified as incoherent paraphrenias and 1 as combined incoherent fantastic. One incoherent schizophrenia was reclassified a phonemic paraphrenia and 3 as speech-inactive catatonias. One incoherent schizophrenia was reclassified as a hebephrenia. Of the 2 paralogical schizophrenias one was reclassified as a manneristic catatonia and the other as eccentric hebephrenia.

Thus 11 of these 21 cases were reclassified in substantially the same way. The misclassification of three speech-inactive catatonias as incoherent schizophrenics can be understood when it is remembered that these catatonics whisper to voices and have an hallucinatory aversion.

Of the 22 cases originally classified as hebephrenias 8 were reclassified as before and 3 were reclassified as combined forms with one component the same as the original classification. Two cases were classified as different hebephrenic subforms and 9 as non-hebephrenic. Thus 11 of the original cases were reclassified in substantially the same group as before.

There are several obvious reasons for these differences in classification. In the first place the two schemes do not coincide to the degree which names of the individual subgroups would suggest. Thus Kleist in his description of progressive hallucinatory somatopsychosis (Kleist, 1947) says that auditory hallucinations recede into the background as the illness progresses, but Leonhard regards a special variety of auditory hallucinations as essential for the diagnosis of hypochondriacal paraphrenia. Quite a number of the author's cases which were originally classified by him as combined systematic paranoid schizophrenias were considered as combined Kleistian subforms because of the vagueness of Kleist's descriptions. These cases when considered in the light of Leonhard's views fitted neatly into one of his groups. Thus 18 cases out of 39 systematic paranoid schizophrenias were considered as combined forms whereas on reclassification only 7 cases out of 48 paraphrenias were considered to be combined forms. This contradicts the author's previous criticism of the Kleist Leonhard scheme of classification (Fish, 1957b). In fact, if one uses Leonhard's criteria then combined forms are not very common.

Another reason for the apparently extensive reclassification is the author's inexperience and methods of investigation. Although the original



107 cases had been briefly surveyed by the time that the author resigned from the staff of St. Nicholas Hospital it was necessary for him to return to the hospital on several occasions to re-examine the patients and carry out tests of thought disorder. Where possible the patient was classified during an interview but frequently it was necessary to consider the protocols very carefully after the patient had been seen and when the author had returned to Edinburgh. When the diagnosis had been narrowed down to two or three possibilities it would have been preferable to make the final decision by seeing the patient again and interviewing the nursing staff once more. However owing to the relative inaccessibility of the patients this was not always possible. It is all too easy to fasten on one facet of the case and not see it as a relatively unimportant part of the clinical picture. Thus in the two cases classified as paralogical schizophrenia, eccentricities and mannerisms of speech were noted and the diagnosis of a severe thought disorder was made. Later it was apparent that these abnormalities of speech were due to catatonia and hebephrenia.

When the cases were reviewed with Dr. Christian Astrup, it was remarkable how often Dr. Astrup and the author independently reached the same diagnosis even if it was different from the author's original diagnosis. In no case was there any gross disagreement between Dr. Astrup and the author on the group to which a given case belonged.

#### SUMMARY

The scheme of classification of schizophrenia described by Professor Karl Leonhard is briefly outlined. The 107 cases originally classified according to Kleist's scheme are reclassified according to Leonhard's scheme. An additional 4 cases excluded from the original series are also classified. In the reclassification the author was helped by Dr. Christian Astrup who saw 103 of the cases jointly with the author. It is concluded that Leonhard's scheme is more precise and easier to use than that of Kleist.

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# A CLINICAL AND METABOLIC STUDY OF ACUTE INTOXICATION WITH *CANNABIS SATIVA* AND ITS ROLE IN THE MODEL PSYCHOSES

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THIS paper describes an inquiry into the effects of giving oral doses of the narcotic drug variously known as hashish, marihuana and, in South Africa, dagga. The drug is a preparation from the plant *Cannabis sativa* whose narcotic effect has been known for centuries. The writer's interest in it was inspired by the work in recent years on the mental disturbances produced by the active principles of other plants, e.g. mescaline and lysergic acid. Because of the similarity of these changes to those occurring in conditions such as schizophrenia, some workers have suggested that these "model psychoses" could be used as a research tool in attempts to elucidate the mechanisms and causes of the naturally occurring psychoses. Although there has been a great deal of work on mescaline and lysergic acid, cannabis has not received much attention. This may be because its chemistry is still not fully worked out and preparations of the plant are difficult to standardize and vary in their potency.

Cannabis is widely though illegally grown in South Africa and there is no difficulty in getting supplies from the police for research purposes.

Because of possible dangers, such as addiction, in using the drug, research was confined to volunteers from the medical staff of Groote Schuur Hospital, the teaching hospital attached to the University of Cape Town. This also had the advantage that all volunteers, being medically trained, were reasonably equipped to describe their experiences under the drug.

As a background to the investigation a brief general history of the cannabis habit is given and a fuller one of the use of the plant in South Africa. The experiments and findings are described in some detail, using the words of the subjects as much as possible. Various physical changes that occurred are described as well as the results of special investigations such as blood-sugar curves and electro-encephalographic changes.

Finally the implications of the findings are discussed.

The work is limited to acute intoxication. Research on the chronic effects of cannabis addiction is badly needed. There is much divergence of opinion about the chronic effects, but this question, and the interesting sociological and legal aspects of the habit are inevitably beyond the scope of this inquiry.

Although the drug is known by various names, for the sake of consistency the name cannabis has been used as far as possible.

## GENERAL HISTORY

One explanation for the name cannabis is given by Lewin (1931, p. 109). He says that the Assyrians used hemp as incense in the seventh or eighth century before Christ and called it "Qunubu" or "Qunnabu", a term apparently borrowed from an old East-Iranian word "Konaba", the same as the Scythian



name cannabis and as the word "Kanaba" which is derived from the primitive Germanic word "Hanapaz". Lewin suggests that these words are identical with the Greek term *κοναβος* meaning noise, and that it would seem to originate from the noisy fashion in which the hemp-smokers expressed their feelings.

The hemp plant, *Cannabis sativa*, source of the narcotic, is a native of Central Asia and is now grown in many parts of the world. It is an herbaceous annual that grows to a height of 4–8 feet or more. The leaves are long, slender and serrated and have about 5–7 lobes arising from the same point, rather like the fingers of a hand spread fanwise. Male and female flowers grow on separate plants. The seed is hard and bony. The plant is covered with glandulose hairs rich in a resinous exudate. The resin contains most of the active ingredient of the hemp, though the seeds also contain a small amount. Traditionally the flowering tops of the female plant have been regarded as the richest source of resin, but this is not now generally accepted. Narcotic potency varies with the heredity of the plant and with the climate—a hot dry atmosphere tends to increase the yield of resin and some people think that this is because the resin has a protective function.

The plant is known by many names. The Chinese call it Ma; the Indians give different names to it according to how it is prepared: bhang, composed of the leaves and sometimes the fruit of the plant, ganja, made from the flowering tops of female plants and twigs covered by resinous exudate, and charas, the most potent preparation, which consists of the resinous exudate secreted by the leaves, young twigs, bark of the stem and even the young fruit of the female plant (Chopra and Chopra, 1957, p. 5); in the Middle East it is called hashish (according to the *Shorter Oxford English Dictionary* the English word "assassin" comes from the Arabic hashisan, meaning hashish-eaters and, later, certain Moslem fanatics who were sent out to murder the Christian leaders in the time of the Crusades); in North Africa it is called kif; in Russia, anascha; in Turkey and Persia, esrar; in Spanish-speaking America, marihuana; in Brazil, macoha; in South Africa, dagga (by Europeans and Coloured people) and mbanzhe, mbangi, matakwane, intsangu, etc. (by Africans).

As a narcotic the plant has interested men for centuries—incidentally, it is also an excellent source of fibre, hence the name hemp.

From early times religions have made use of it. The Hindus regarded it as a holy plant and had many legends about its origin, such as that it was brought out of the ocean by the god Shiva and all the gods churned it in order to extract "nectar" from it. Much of the sanctity attached to the plant was due to the belief that it "clears the head and stimulates the brain to think".

Some of the Mohammedan sects regarded the plant as an embodiment of the spirit of the prophet Khizer Elijah, the patron saint of water (Khizer means green, the colour of the drink made from bhang) (Chopra and Chopra, 1957).

The lives of some tribes in the Congo centre on hemp, which is cultivated, smoked regularly and venerated. Whenever the tribe travels it takes the Riamba (huge calabash more than a yard in diameter which is used for smoking) with it. The man who commits a misdeed is condemned to smoke until he loses consciousness (Lewin, 1931, p. 114).

Apart from its use in religions it has been widely employed as a medicine. Its main therapeutic properties have been considered to be analgesic, sedative, anti-spasmodic and diuretic, though it has been recommended for a host of ailments both internal and external.

It was apparently introduced into Western medicine at the beginning of the 19th century by doctors attached to Napoleon's occupying forces in Egypt. They were sufficiently impressed by its sedative and analgesic properties to use it in the army, though the French generals were so appalled by the habit among the natives that they introduced several regulations forbidding its use.

Its use then became fairly widespread in Western Europe and it has been estimated that between 1840 and 1900 more than 100 medical articles were written recommending it for various ailments (Walton, 1938, p. 152).

Besides medical interest, it became fashionable among certain writers, artists and intellectuals to take cannabis as a "lark". Many of these people came to use it regularly and have left colourful accounts of its effects.

There were in the 19th century few alternatives to opium as a pain reliever, but by the beginning of the present century interest had shifted to new drugs, and sedatives such as chloral hydrate, paraldehyde and the barbiturates were being widely used. Cannabis preparations had always been difficult to standardize and if kept for long tended to deteriorate.

In addition, the chemistry of the active ingredients of cannabis had long eluded analysis.\*

The difficulties of chemical studies of cannabis appear to have been enhanced by a series of unfortunate accidents to chemists engaged in such work. Walton (1938, p. 187) says that "Wood, Spivey and Easterfield, the Cambridge chemists, were not able to complete their program because of a series of tragic accidents. Wood barely escaped with his life when he took some cannabinalol at the time he was preparing zinc ethyl. He lost consciousness, the zinc ethyl ignited and he was rescued from the burning room only with much difficulty. Easterfield was killed in a violent explosion while attempting to hydrogenate cannabinalol. Spivey similarly perished while engaged in a synthetic study of the nitro-cannabinalactone."

The pharmacological action in animals is poorly understood. The main action is on the central nervous system and ataxia potency in animals closely parallels psychic potency in man. Samples of the crude material are such a mixture of different fractions that they vary considerably in their potency. Loewe (1950) is an authority on the chemistry and pharmacology of the crude extract and the synthetic preparations. He found it poorly soluble in water and it dissolved slowly even in ideal solvents such as acetone. Consequently it is absorbed slowly. Even after intravenous injection, 30-60 minutes may elapse before a peak effect is attained and the effect may persist for hours or even days. The margin of safety is enormous. Despite the wide use of the drug only two cases of death in human beings have been reported. Ewens (cited by Walton, 1938, p. 126), reported two cases from India in which a large overdose

\* Goodman and Gilman (1955) state: "the isolation of the active principles proved most difficult. For many years it was erroneously believed that cannabinalol, discovered in 1899, was the active principle of hemp. Cannabinalol is a homogeneous, viscous oil obtained from purified 'red oil' derived from hemp extracts or resin. The chemical structure proved to be a dibenzopyran derivative. Cannabidiol was soon isolated from fresh hemp extracts and its structure identified. Cannabinalol is the product of an inner condensation and reduction of cannabidiol. The former is virtually and the latter entirely inactive pharmacologically, but cannabidiol provides the basis for the synthesis in the laboratory of products of high potency which are probably isomers of the active principles of the red oil of hemp. Although reports of the isolation of natural active compounds and their derivatives have appeared it was not until 1942 that Wollner and his co-workers isolated and identified a natural tetrahydrocannabinalol. This compound is quite active in animals and man, as is also a number of its synthetic congeners. The tetrahydrocannabinols are the intermediate products in the conversion by the hemp plant of cannabidiol to cannabinalol. Approximately 80 derivatives of tetrahydrocannabinalol have been synthesized and studied pharmacologically."

proved fatal. Ewens said "the effect was rapid coma with vomiting of green-coloured contents of the stomach, stertorous breathing, etc. with marked congestion of the conjunctivae and coldness of the body surface. At post-mortem there was a most curious congestion of all the internal organs of the body". Dogs have been killed with large doses of one of the synthetic cannabis preparations and the most striking autopsy finding was profuse intestinal haemorrhage; after intravenous injection the dogs developed fatal pulmonary oedema. (It is well known that both these findings sometimes result from acute cerebral disease in humans).

With more potent synthetic preparations of cannabis, death is associated with convulsions and appears more directly due to central nervous system damage.

Investigation into the chemistry of cannabis stimulated fresh clinical interest in the drug. In 1938 Walton wrote a comprehensive book on marihuana; in 1939 Bromberg described mental reactions seen during intoxication with the drug; in 1941-1942 Adams reported on the co-operative work of three laboratories—chemical, pharmacological and clinical; in 1942 Allentuck and Bowman described the psychiatric aspects of cannabis intoxication; in 1944 a team of workers, including doctors and police officers, issued a report on it in New York and the results of their experiments with 77 subjects, and in 1957 the Narcotics Division of United Nations Publications issued a full report on cannabis in India.

Occasional reports on the therapeutic use of cannabis have appeared in recent years. In 1947 Stockings described synhexyl, one of the synthetic cannabis preparations, as a "new euphoriant". He used it in 50 cases of "neurotic depression" and claimed that 36 showed definite improvement: their depression lifted, they had an increased zest for work and were more accessible to psychotherapy.

Parker and Wrigley (1950) tried synhexyl in 62 cases of melancholia and neurotic depression giving 10-20 mg. daily. They were not impressed by the drug after using the "double-blind" method, but despite this concluded their paper by saying that it is undoubtedly a euphoriant and further work should be done on it.

In 1954 Rolls and Stafford Clark described the successful use of cannabis in the treatment of a case of depersonalization. They included cannabis in the group of hallucinogens described by Osmond and Smythies (1954) and discussed its possible mode of action.

#### SOUTH AFRICA

Cannabis was in use for many years before Europeans settled in the country and was smoked by all the non-European races, i.e. Bushmen, Hottentots and Africans. It was probably brought to the Mozambique coast from India by Arab traders and the habit, once established, spread inland. The similarity of African names for the drug, e.g. mbangi, to the Hindi bhang, suggests this mode of entry into the country.

The term "dagga" is derived from the Hottentot "dachab"\* and is applied

\* Senator Vedder, who has lived in South West Africa for many years and is an authority on the customs and language of the native inhabitants, says that the term dagga originates from the Hottentot—dachab being the singular and dachagu the plural. The term can be explained in two ways. Firstly, dacha is an Arabic word meaning "to smoke". Secondly, in the Hottentot language "da" is a verb meaning "to tread down". If "cha" is added to a verb the word receives an additional meaning that you do it with pleasure and frequently, e.g.



not only to *Cannabis sativa* but also to *Leonotis leonurus* (Red or Wilde dagga) and *Leonotis leonotis* (klip-dagga). These two plants are reputed to have a mild narcotic effect (Gunn) but are not generally used for that purpose although they are apparently given to animals, e.g. racehorses, as a stimulant.

The plant has been used for many purposes in South Africa. Suto women smoke it to stupefy themselves during childbirth; they also grind up the seeds with bread or mealie pap and give it to children when they are being weaned (Watt and Breyer-Brankwijk, 1932). It has often been recommended as a local application for snake-bite and some "cancer curers" use the oil from a dagga pipe as an external application. It has also been recommended for malaria, anthrax and dysentery.

Apart from African folklore there are four studies by Europeans on the use of cannabis in South Africa. The position before 1913 has been described by Bourhill. According to him dagga smoking was widespread among rural Africans and did not constitute a problem. Only adult males were permitted to smoke. They did so in a leisurely manner and smoking was often accompanied by the "dagga games". These games were played by blowing saliva through thin reed pipes to create intricate patterns. When the smoke was inhaled through water (the customary way of smoking) excessive salivation (it was claimed) was induced. The old men of the tribes gave their fondness for these games as one of the main reasons for continuing dagga smoking.

Bourhill states that dagga smoking was not only permitted but actually encouraged among African mine-workers because "after a smoke the natives work hard and show very little fatigue".

The usual mine practice was to allow three smokes a day. Nevertheless, the impression was growing even at that time that dagga smoking was harmful to urban Africans. Bourhill's discussion of this view naively reflects social attitudes to Africans at that time. He accepted uncritically the current belief that Africans were unstable and inferior in intelligence.

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ma means to give and macha to give gladly. Consequently, dacha might mean "to tread down gladly or frequently", i.e. the dagga smoker gladly becomes stupefied. Senator Vedder is of the opinion that both the Arabic and Hottentot languages have contributed to the name of the plant though many people might consider the Hottentot derivation given as rather too tortuous. Vedder tells a favourite story about dacha. Apparently in Karibib there was a Bergdama (one of the native people) who decided to surround his hut with a new kind of verandah. He placed barrels in a semi-circle round the hut and filled them with earth. On top of them he placed another layer of barrels so that the wall was more than the height of a man. In the top barrels he planted dacha plants. Many police passed but did not know what went on. When the plants had grown he cut them, plaited them, rolled them and fastened them with long thorns. Nobody disturbed him in this work. But a young Bergdama watched him and asked for an explanation. The old man said that the plant was dacha that could be smoked. The smoker would then enter into a wonderful sleep and see things that one did not normally see and he would receive a wonderful feeling of happiness and contentment. The young man asked for a pipeful of this wonderful stuff, filled his pipe and returned to his pondok to smoke it. But it did not take long before he put down his pipe, and very tired he sank into a deep sleep. When he awoke he was berserk.

In olden times the Bergdama used the plant for magic rites. They appointed one from their midst to smoke himself to sleep and his friends would watch him. If he smacked his lips they would say they could expect a year when they would find much wild honey, but if the smoker looked sad it was a foreboding of a bad year.

These people also used to dance a folk dance to an old song about dachab:

"The water bubbles O dachab  
You little seed which grows because of the water  
The bushy tail fed by the spring  
You cover the earth—you sit in my head  
The dachab from the river has got hold of me  
Show me a kudu O dachab  
So that my hunting will be successful", etc.

He paints a reasonably accurate picture of acute intoxication with cannabis, though it is doubtful whether auditory hallucinations are, as he claimed, part of the picture.

The second part of his paper dealt with "dagga insanity" among patients admitted to Pretoria Mental Asylum during the years 1908 to 1912. He claimed that 18 per cent. of all males admitted during this period were suffering from "dagga lunacy". In a review of 103 cases the average age was 27, the average period of detention in the asylum 255 days and relapses occurred in 41 of the 103 cases.

Bourhill's labelling of his cases as "dagga insanity" is not acceptable. He himself mentions the difficulty in excluding alcohol as a factor and there is no good reason why many of his cases might not have been schizophrenics who were also cannabis smokers. His emphasis on auditory hallucinations is much more suggestive of schizophrenia than cannabis intoxication.

In 1936 Watt and Breyer-Brankwijk cleared up much confusion about the plants to which the name "dagga" applied by showing that *Cannabis sativa* was "true" dagga with undoubted narcotic properties while the other plants called dagga belonged to the *Leonotis* family, i.e. klip-dagga, wilde dagga, etc. Only one species, *Leonotis leonurus*, had been investigated (Gunn) and was reported to be mildly anthelmintic, feebly narcotic and probably harmless when smoked.

Watt and Breyer-Brankwijk described some of the clinical effects of smoking *Cannabis sativa* and urged a controlled investigation into the relationship of the cannabis habit to the production of acute psychosis and of permanent mental deterioration.

The third paper appeared in 1938 as the result of this suggestion by Watt and Breyer-Brankwijk. It was based on an investigation by the medical staff of Pretoria Mental Hospital on 72 non-European patients (22 of whom had been diagnosed as "dagga psychosis"). The patients were observed while smoking cannabis and the results recorded.

The writers found that all cases showed marked mental dulling; 35 per cent. of the cases showed motor excitement; 45 per cent. reacted with depression and 20 per cent. "just became silly and fatuous". The authors themselves seem to have been doubtful about the information that could be gleaned from this experiment as all the patients were psychotics and some of the effects observed might well have been due to activation of the original psychosis.

The fourth paper, 1951, is a report by a committee appointed by the Government. It is not confined to the medical aspects and is, in fact, full of valuable information and gives a balanced history and assessment of the problem as a whole. The committee felt that the picture of acute dagga intoxication was fairly well known but that there was far too little information on the effects of chronic dagga smoking. The committee pointed out that since 1928, when the cultivation of dagga had been declared illegal, there had been an unceasing prosecution of those engaged in the trade. They found it impossible to give an accurate idea of the extent of dagga smoking in the Union of South Africa, but felt that the practice was widespread among Africans (both rural and urban) and less common among the Coloured people and Europeans. Of all persons prosecuted for dagga offences, Africans regularly constitute 75 per cent., although many of these are traffickers who do not themselves use the drug.

#### EXPERIMENTAL WORK

The investigation which is the subject of the present paper was designed to study the effect of giving a single oral dose of *Cannabis sativa* under controlled

conditions. All subjects were medically trained and the writer had known them for some time before deciding to use them in the experiment so that on the whole they were articulate and fairly stable people.

The work can be divided into five sections:

1. This deals with the effect of cannabis on 10 subjects (two female) in the 20–30 age group. Seven subjects were asked to participate and three volunteered spontaneously. They were all interns with no particular knowledge of psychiatry or chemical intoxications. During the experiment particular attention was paid to
  - (a) Subjective experiences and behaviour;
  - (b) Clinical changes;
  - (c) Certain special investigations, e.g. half-hourly blood-sugar estimations, urine output, electro-encephalographic recordings before and three hours after the cannabis had been taken.
2. The experiment was repeated on three subjects but on this occasion blood sugar estimations and electro-encephalographic recordings were not done.
3. The writer took cannabis but did not have blood-sugar estimations done.
4. One subject was inadvertently given an overdose and his reactions are described separately.
5. Four male cannabis addicts were interviewed.

#### TECHNIQUE

All the subjects knew that they were taking cannabis and took full responsibility for their actions.

They fasted from 10 p.m. the previous day and presented themselves in the ward at 8.30 a.m. On arrival an electro-encephalographic recording was done, blood was taken for blood-sugar estimation and the subject got into bed in pyjamas and a basal pulse rate was established. An oral dose of cannabis was taken without water. The dose varied between 4–7 grains according to body weight and temperament. An observer stayed with the subject more or less continuously (in all cases the writer and one other person acted as observers, relieving each other when necessary). The observers took notes throughout the experiment and sometimes took a tape-recording or took the pulse rate if the nurse did not arrive at the correct time. In addition, blood was taken from an arm vein every half-hour and urine output was measured before the experiment began and three hours after it had started.

A second electroencephalogram was done three hours after the cannabis had been taken and three to four hours afterwards the subject was given a meal and left to sleep and drowse through the rest of the day with occasional visits.

All but two (one of whom was the writer) of the ten subjects were kept in the ward overnight. The two who returned home were driven home, one at 10 p.m. and the writer at 5.30 p.m.

All subjects submitted a report within the next few days on what they remembered of the experience.

#### PREPARATION

One thousand grammes of powdered *Cannabis sativa* was extracted by the method given in the British P.C. (1934, p. 1229). The product yielded 110 grammes of concentrated resinous extract. Of this extract sufficient was taken



to make 1,000 pills, each containing 0.06 grammes of extract, using powdered liquorice root and powdered tragacanth as excipients. Each pill, therefore, contained one grain of *Cannabis sativa*.

A healthy female cat was given 6 grains of the extract of the *Cannabis sativa* made up into an emulsion with Pulv. Trag. Cr. Within two hours a change in its behaviour was noted in that it seemed disinclined to move and remained looking apathetic on the floor of its cage. When taken out and encouraged to drink it exhibited marked ataxia and had great difficulty in lapping, continually hitting its head against the side of the saucer, splashing the milk, etc. It remained apathetic for the rest of the day and made a perfect recovery on the following day.

## 1. (a) SUBJECTIVE EXPERIENCES AND BEHAVIOUR

### General

The onset of the abnormalities of sensation was always abrupt and unmistakable. All subjects were somewhat apprehensive at the beginning of the experiment and anxious to report on every change. But once the drug really took effect there was no doubt about the reality and definiteness of the change.

A. after complaining hesitantly of various vague symptoms suddenly said, "This is it", and immediately lay down because of light-headedness and a feeling of unreality. He reported, "With me the first perceptual change was a change in the colour and outline of objects. Colours became striking and vivid—the curtains were a vivid green, the room looked freshly painted and the figures in the room looked as if they had been cut out of cardboard. There was no third dimension. They were flat with bright colours and sharp outlines, and were seen through a screen of moving black dots like a newsprint photograph, with moving dots instead of still ones."

B. also experienced an abrupt onset accompanied by marked physical changes. He said, "I had been waiting for the first symptom with some curiosity. I thought I noticed a mild weariness and an aching feeling, mostly in my neck and shoulders. I was just saying perhaps this was something definite when I was 'hit' by fairly violent somatic symptoms. There was now no longer any doubt that I felt abnormal. I felt less inhibited and was no longer reluctant to talk about myself. The somatic symptoms were waves of warmth which started in the centre of my abdomen and radiated up, fading out about mid-chest. This was associated with forceful, fast palpitations, dyspnoea, dry mouth and waves of throbbing frontal headache." He likened these physical symptoms to adrenaline release "qualitatively the same but quantitatively more violent—it was like having the visceral effects of panic and a mental sense of panic without cause and without alarming thoughts in my head".

The onset was usually accompanied by tachycardia which was often considerable, e.g. pulse rates of 130 were not unusual.

Another striking feature about the experience was that it came in waves and several of the subjects felt compelled to communicate this fact by drawing a line rising and falling. Each dip in the curve might last only a few moments. C. after describing the onset, said a few minutes later, "Well I'm blowned—it's gone—like a colour film with the shutters coming down." Within a matter of minutes he said, "Here I go again—it's a floating away—like a balloon taking off—momentarily it's a positive exertion even to breathe, and yet it is lovely. What a silly thing to say—my emotions seem to have become dissociated from my speech but I feel I must keep on talking to keep human contact." This

subject also described the wave-like alteration in consciousness as "like seeing reality in glimpses as one drives past a row of palings".

Other subjects interpreted the waves of abnormality as sleep. D., suddenly speaking after a few minutes of silence, said, "I was asleep then, wasn't I?" B. would repeatedly fall silent for a moment or two then say: "I keep going off or going away from the room and the observers. I feel that if I keep banging myself I could keep in contact more easily. It reminds me a bit of driving in the early hours of the morning along a monotonous road when one is very tired."

E. said, "I had phases of losing contact with reality and at times I did not know whether I was awake or dreaming, but when I surfaced everything was quite clear."

These lapses lasted a few minutes but to the subjects they seemed an eternity. Their minds were not occupied with anything in particular at these times, except for those subjects who, on closing their eyes, saw visual images.

During these lapses the observer could always rouse the patient to give relevant replies to questions but the demeanour and intonation of the subjects suggested great languor and was in striking contrast to the briskness and alertness of the emergent phases. C. said, "Now I am in full possession of my senses—my mind is precision clear."

The mood was usually one of detachment and mild amusement. The subjects, after emerging from one of these wave-like experiences, described what had happened without apparent anxiety.

### *Thought Disorder*

Several subjects described their thought processes as "fragmented". One subject, F., in whom this was accompanied by extreme anguish said, "There was no blunting of perception and no distortion, but before I could express a thought by word or action it was lost to me and displaced by another and often irrelevant thought. I thus had extreme difficulty in sorting out thought processes to a single idea goal."

Several subjects felt they were thinking more efficiently than usual. C. said with deliberate emphasis, "There is no mental or physical feat of which I do not feel capable." D. said, "I am enjoying talking because so many new associations occur to me—my talk is disconnected only because I immediately forget previous statements." G. felt that he was acquiring deeper insights into his basic personality structure, that he had a new awareness of the meaning of things; yet in the next breath he said, "My thought processes are slow and I have difficulty in expressing myself—it's like dysphasia—I've read a paragraph 4 to 5 times and it won't stick."

B. complained that he could not get the meaning of a simple cartoon he was looking at, and several subjects stared for many minutes at a book, puzzled because it had suddenly become meaningless.

One striking change was a loss of recent memory or rather a difficulty in recall. Because of this, conversation became bizarrely disconnected. If a subject was asked a question about a statement he had made a few seconds earlier he was often unable to answer because he had forgotten what he had just said. When reminded of it he immediately took up the thread of conversation, saying, "How odd—I remember it now, but before it was lost to me." Direct questioning invariably elicited prompt and relevant replies and in most cases the 7 from 100 serial test was well done, but if subjects were left to themselves to pursue a train of thought this difficulty of immediate recall manifested itself.

Despite this the notes kept by the observer and the notes written by the subjects a day or so later corresponded very closely and in no instance was anything considered important forgotten.

Several subjects were struck by the dissociation between thought and action, e.g. F., when asked to sit up said, "I never thought I would be able to sit up—it is almost as though my muscles held me up without volition."

### *Delusions*

Several subjects became suspicious during the experiment. H. refused on several occasions to close his eyes because he thought he was being hypnotized into seeing visual images. C. often paused before answering a question and admitted that he was examining it for hidden implications. He asked uneasily several times, "Is there someone hidden behind that screen?" I., at one time was convinced that a tape-recorder had been concealed in the room and talked into the imaginary recorder when left alone for a few minutes.

A. got very suspicious when someone came in to hand the observer the electrocardiogram of a patient—he was convinced that it belonged to him (an E.E.G. had been done on him), was abnormal and that this information was being withheld from him. He was eventually convinced by being handed the tracing with someone else's name on it.

J. became convinced that cannabis had unmasked a latent schizophrenia and when several people came in to talk to him he refused to answer any questions because he believed they had been called in to certify him. When the second EEG was done on him he was convinced that he was receiving electro-convulsive therapy in spite of the fact that three hours earlier he had been through exactly the same routine for an electro-encephalographic recording.

### *Temporal Orientation*

All subjects experienced a disorder of temporal orientation and it gave a remarkable quality to the experience. Events occurring immediately after each other seemed separated by an eternity of time, e.g. B. said, "The puffs between cigarette smoking seemed an eternity", and D. said that a venipuncture which had taken under a minute seemed to take about fifteen minutes. Several subjects asked uneasily when someone had just left the room, "How long is it since he left?" and were astonished at the answer because they thought it was so much longer.

Subjects could never estimate the time correctly. They invariably made an error ahead, i.e. they always thought it was much later than it was. One subject thought it was afternoon and not morning and another said he would not have been very much surprised if it had been the next day.

Because of this temporal disorientation distances seemed much longer, e.g. when subjects were wheeled down the corridor they felt that the journey was immensely long.

### *Disturbances of Visual Perception*

Four subjects experienced disturbances of visual perception. A. said that people looked as though they were cut out of cardboard. He later described the face of one of the observers as "like an alabaster tortoise", and another as "sharply delineated through a blue haze of cellophane with acne showing up as pink excrescences and the head two or three times bigger than normal".



H., while laughing hilariously, said to the observer, "Your eyes look like large oranges—as big as a beach umbrella."

B. described one of the observers as looking like "an Egyptian pharaoh in judgment" and the ceiling as having "an iridescence like mother-of-pearl", while some wire netting formed a "rather pleasing pattern—benzene rings or stained-glass windows with two lots of colours—emerald green and grass green and red and green".

D., watching the sun's reflection on the wall, said, "It looks like a hyena or a duck-billed platypus."

### *After-image*

Many subjects seemed to experience a greater intensity and duration of after-images, especially when objects such as windows had been looked at just before eye-closure.

### *Visual Hallucinations*

Six subjects experienced visual hallucinations but only when their eyes were closed and usually when they were experiencing a disturbance of consciousness. H. said, "Now I see gold with blue and red stripes—flickering lights and patterns like a cartoon. Now it is changing into a technicoloured cartoon with a silver ray going up into the sky". Later he said, "Whenever I shut my eyes I lose control and see my brain like a ballerina's dress going round and round in the middle of a glass cube. A. said, "I see a cross-pattern of people in old European costume—it changes so quickly—it has already changed a hundred times. Now I see a fat man in military costume running down some stairs. He is in a military uniform, has a snow-white beard and he is in a Roman tunic."

D. said, "I see church windows and mathematical shapes, mainly on the left. Now a meteor—a fiery ball that came and went."

C. said, "I see very beautiful, vivid colours like illustrated thoughts. Now there are little Chinese scenes like lace patterns—very formalized and lovely."

I. said, "I can see fixed prismatic colours racing over my head. Now intricate figures and symmetrical scenes—each half of the picture like the other as though carved out of ivory and lighted from behind. Now it has changed and I see a block of flats with a garage and stable gates and a man is leaning on the gate—it keeps changing and there are flickering bands of light going across like a forked flame."

G. had a variety of visual images. "There is a reddish glow when I close my eyes. I imagine a cat curling up—I don't like cats or scorpions—coloured lights. All based on a pattern—basic theme of glowing, with circles getting larger and larger—there seems to be a cat with long talons curled up crouching on top of me." About 20 minutes later he said, "Imagine a fellow draped like an Egyptian mummy—picture myself on a slab like a mummy—shaft of light" . . . "My teeth feel sore—feel full of holes—that damn circle keeps coming back . . . I rose out of that sarcophagus. Now there is a vague image of a ship in harbour—glowing light on the ship."

All the subjects emphasized the fleeting nature of visual images, the speed with which they changed and the inadequacy of language to describe them properly. If beautiful, they were indescribably so—the colours were of an intensity never experienced before and the patterns marvellously intricate and suffused with light. G. was the only subject who experienced unpleasant imagery,

but when asked if it frightened him he said, "I did not like them, especially the cat, but then I don't like cats but they never actually frightened me."

The general detachment concerning the images was exemplified by several observers who described them as looking like theatre scenes.

### *Disturbance of Perception of Body Image*

B. said, "I had a series of recurring unpleasant feelings about the shape of my own body. One was that my ribs seemed big and thick and sticking out through shrunken flesh like an anatomy body. Another was that two fairly trivial scars on my body sustained in childhood seemed so enormous that they were almost the whole of me. A third disturbance was that my penis seemed deformed. I have the idea it seemed wooden with a clubbed end but it was not erect."

C. said, "My one eye feels bigger than the other—like a Picasso picture—my face is drawing out like a Greek mask and when the corners of the mask go up I feel happy."

H. said, "In the beginning I had a pleasantly warm feeling beginning in the umbilical area and extending down both legs and genitalia—not erotic but a delightfully soothing feeling. Later I soon realized that I was having a watered-down orgasm which was constantly present—a most delightful feeling. But at the same time I seemed to have lost all sensation from my bladder and penis and had no control over the sphincter muscles or erectors and can remember being acutely disturbed as to whether I was disgracing myself by passing urine, faeces or semen into the bed. I had no idea whether I was wet or not, except by looking to see." (We had great difficulty in getting urine from this patient—he felt quite incapable of passing urine because his urinary apparatus seemed dissociated from him.)

F. experienced three attacks of what he described as "a sort of vertigo. I feel I am travelling a spiral course in a forward and up and down direction and the spirals are gaily coloured and all this is accompanied by coloured vertiginous thoughts." Each of these attacks was accompanied by acute anxiety and only occurred when his eyes were closed. This subject also complained of a "fluid-like feeling in my mouth—like a pad—it seems to make it difficult for me to articulate. Yes, it is amorphous—How amorphous can one get." (This remark accompanied by much merriment.)

I. said, "My body feels as though it is in continual motion, rocking and spinning around through space. My teeth feel strange as though they are made of plastic."

A. complained bitterly of a "horrible vibration" through his body and of difficulty in moving his tongue because it seemed "structureless". He said, "From time to time I get a feeling of descent. I could see a mental image of myself folded like a jack-knife falling through space between triangles of vivid colours set at angles and depths at variance to each other."

### *Depersonalization*

B., summing up, said, "The outstanding psychic experience was a loss of feeling real, an inability to know that I was really doing specific acts like talking, passing urine, etc."

F. said he had a curious double image of himself. "It is as though I am watching myself lying in a big transparent bubble with my face pressed close to the side."

C. and I. both likened the experience to watching a film of one's own performance.

H.'s difficulty in knowing what his body was doing has already been described.

### *Mood*

Mild euphoria was present at some time in all subjects and often one of the first abnormalities noted was a sudden unexpected burst of laughter because the whole idea of the experiment seemed suddenly very funny, or because some mildly amusing occurrence had become uproariously amusing.

On these occasions subjects would be unable to restrain their mirth, which was usually infectious.

One subject became extremely distressed about his "fragmentation of thought" and begged in anguish to have the experiment terminated immediately because everything had suddenly become unreal and terrifying—"this is like schizophrenia—there is a blocking between emotion and thought and it frightens me." His agony lasted only a few seconds and during this period the observer felt quite unable to make contact with him. Within a few minutes he was euphoric and with a laugh said, "In a way I can understand why people take it—if you just let your thoughts drift without worrying about them having reality or meaning it is quite relaxing."

Two subjects felt that the whole experience was extraordinarily delightful. J. said, "It is such a lovely drifting voluptuous sensation", and C. said, as the experiment was coming to an end, "I've got such a let down feeling—it is like coming out of a golden dream." These two subjects were the only ones who felt they would gladly take the drug again.

A curious detachment was common. At times the observer would become quite disturbed about some unexpected occurrence, e.g. gross muscular contractions, inability to urinate, sustained tachycardia of 140, or expiratory dyspnoea, etc., but the subject, although aware of the occurrence, seemed insulated from anxiety about it. Some of the subjects mentioned headache as one of their symptoms, but when asked if it bothered them they laughed and seemed as detached as if it were someone else's headache. This detachment also extended to disorder of mental functioning, e.g. loss of recall, seemed amusing more than alarming. If they had difficulty with a test they usually shrugged lazily as if to say, "What does it matter anyway?" Four subjects showed anxiety, but even then it was mild, or very transient, except in F. This was well shown by J., who became convinced that cannabis had unmasked a latent schizophrenia and that the second EEG was really electroconvulsive therapy, but this delusion was accompanied by what he called "uneasiness" even though he had thought out all the implications of being psychotic, e.g. losing his job, the distress of his parents.

Although this is the most striking example, all subjects showed inappropriateness of affect at some stage. G., while complaining bitterly of painful muscular spasms, burst out laughing.

After several hours, when the effects of the drug were wearing off, most subjects felt apathetic, disinclined to talk and vaguely depressed.

### (b) CLINICAL CHANGES

#### *Physical Symptoms*

An invariable complaint was marked dryness of mouth. This was often one of the first symptoms noted. All subjects complained of paraesthesiae



in the fingers and toes; five subjects also complained of paraesthesiae over the nose and round the mouth.

Several subjects described a "warm glowing feeling" which was experienced in the abdomen or pelvis.

Several subjects complained of intense praecordial discomfort.

Two subjects complained of expiratory dyspnoea.

### *Signs*

A most interesting and striking feature was a uniform suffusion of the conjunctiva sometimes accompanied by oedema of the eyelids. This invariably appeared about one to two hours after ingestion of the drug and persisted for many hours. It was not accompanied by any subjective discomfort and did not wax and wane. All subjects developed a sinus tachycardia—in one case the pulse rate, initially 56, rose to 80, but in all the other cases the rate rose to between 120 and 140. An ECG was done on one case and the graph showed a sinus tachycardia. In most cases the tachycardia persisted for several hours before the pulse gradually returned to its original level.

There was occasionally some rise in blood pressure in the first hour or two but this was never excessive, mainly systolic, and never exceeded 160 mm. Hg.

All subjects developed moderate coldness of the extremities and in some cases fingers and toes looked pallid.

One subject (a blonde) developed patchy flushing of the skin over the face and upper trunk which persisted for some hours.

Five subjects complained of mild frontal headache.

Nausea was common, occurring about 3 hours after the start of the experiment and some subjects vomited. It was the writer's impression that this symptom was related to the moving of the subject to the laboratory for the second EEG recording. The impression was that any movement at this time aggravated vasomotor imbalance. Subjects frequently became very pale and cold, but after returning to bed and being warmed, or after vomiting, they improved rapidly.

No subjects complained of hunger during the first three hours although they had not been given anything to eat or drink since 10 p.m. When given food all ate with relish—five said, "Even hospital food tastes delicious."

Reaction to venipuncture was variable. J., after the third puncture, begged to be allowed to discontinue the blood-sugar estimations because they were "agonizing". F., after the third puncture, said, "It's amazing—the drug is an analgesic—I did not feel a thing though I watched all the proceedings." Most subjects thought that the needle pricks became more and more unpleasant, but quickly added that it may well have been a cumulative effect.

### *Abnormal Movements*

Paucity of movement was usual and subjects ascribed this to the feeling of tranquillity and detachment. In many cases it was even an effort to speak and the observer had repeatedly to stimulate the subject by asking questions. Several subjects expressed their astonishment at the thought of anyone being impelled to violent or aggressive action by the drug.

G., however, exhibited the most astonishing muscular movements. These consisted of gross flexion-extension and abduction-adduction movements, principally of proximal muscles of the lower limbs and all muscles of the

upper limbs. The movements could be stopped momentarily if he were urged to do so but immediately began again and were accompanied by much discomfort and complaint of soreness. "This is real—this is motor cortex irritation not hysterical. No, it is not a convulsion—my knee is dancing a Scottish reel." There was a certain amount of facial grimacing at the same time and a curious struggle between laughter and tears. The movements continued virtually without cessation for about three hours and the subject was left with painful, aching limbs the following day.

A. periodically gave a sort of jump with arching of the back and said it happened when he got a "vibratory feeling" passing over his whole body.

F. complained of involuntary muscular twitching involving at different times proximal limb or abdominal muscles—visible to the naked eye but not gross enough to move a limb.

### *Muscular Co-ordination*

Most subjects complained of slight difficulty in articulation but this was seldom objectively demonstrable. Crude tests such as the finger-nose test were usually well done, but picking up a small pin was difficult. The gait was not strikingly ataxic but subjects felt light-headed when walking and did not show any alacrity about getting out of bed for some hours after the drug had been taken, e.g. D. said, "About 8 hours after the start I thought I would have a bath but felt so unsteady when I got out of bed that I decided to sleep instead."

## (c) SPECIAL INVESTIGATIONS

### *Electroencephalography*

Parasagittal and temporal recordings were done before cannabis was taken and repeated three hours afterwards. Of ten recordings four were reported as showing no change and in six there was some change. The reports were as follows:

- E. The resting record shows a well-marked persistent 9 c.p.s. alpha rhythm in occipital and central areas.  
After cannabis the only change is a slight tendency to diminished persistence with longer and more frequent intervals of fast activity. EEG—slight change towards less persistent alpha after 5 grains of cannabis.
- J. The resting record shows a well-marked, persistent and well-modulated 9 c.p.s. alpha rhythm which is present diffusely, except in the frontal areas where beta activity is seen.  
After cannabis the occipital alpha remains largely unchanged except that it is not quite so persistent and there is some intervening fast activity with a little random alpha over the post-central areas. EEG shows some change after cannabis—tendency to replacement of non-occipital alpha by fast activity.
- G. The resting record shows a 9 c.p.s. alpha activity posteriorly, most persistent in the temporal areas and with a fair amount of fast activity in the parasagittal leads. The only change after 7 grains of cannabis was one very short episode of 6 c.p.s. activity that appeared in the posterior temporal areas.

- H. The initial recording shows a well-marked and almost persistent 10 c.p.s. alpha rhythm posteriorly, of rather low voltage; and low voltage beta activity anteriorly.  
Three hours after taking 7 grains of cannabis the persistence of the posterior alpha activity is considerably less, it being interrupted by much irregular fast activity. The generally low amplitude remains unchanged.
- K. (Clinical record of this case was not included in the series.)  
The record shows generally low voltage fast activity throughout; there is a minimal amount of posterior 11-12 c.p.s. alpha activity. After cannabis the only change is that there appears a moderate amount of bilaterally synchronous anterior temporal 6-7 c.p.s. activity.
- C. The resting record shows a well-marked and persistent 10 c.p.s. alpha rhythm posteriorly with beta activity anteriorly. Three hours after the ingestion of 6 grains of cannabis there is a slight quickening of the alpha rhythm to 11 c.p.s. and it is not so persistent and uninterrupted. The temporal leads show fast activity throughout—probably much muscle artefact.

### *Blood-Sugar Readings*

Fasting blood-sugar estimations were done every half-hour for two and a half hours. These did not show any significant change. There was occasionally a tendency for the blood sugar to show some slight elevation about one hour after the cannabis had been taken but this was never outside the range of normal. (See graph.)

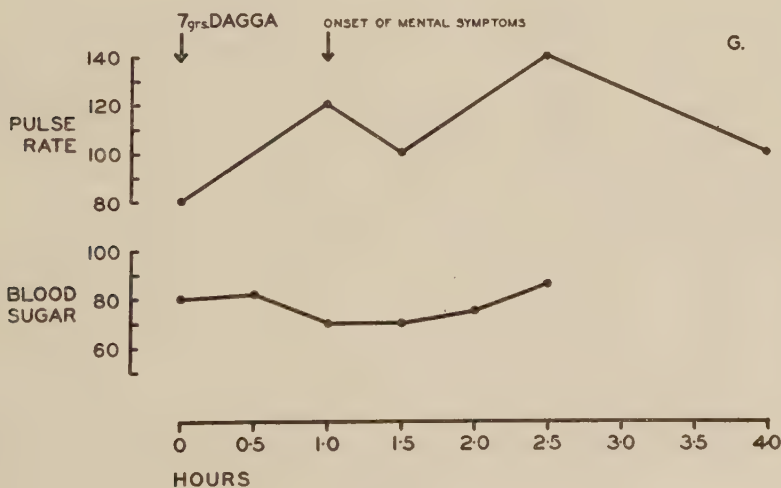


FIG. 1.

### *Urine Output*

Because of the frequent references in the literature to a possible diuretic property of cannabis it was decided to measure urine output during a fixed period before cannabis was taken and for another fixed period after it had been taken. The following table gives the results in seven cases:



| Subject   | Before Cannabis was Taken |                 | After Cannabis was Taken |                 |
|-----------|---------------------------|-----------------|--------------------------|-----------------|
|           | Period of Time            | Volume of Urine | Period of Time           | Volume of Urine |
|           |                           | ml.             |                          | ml.             |
| A ..      | 2 hours                   | 160             | 2½ hours                 | 352             |
| B ..      | 2 hours                   | 224             | 1 hour                   | 569             |
| C ..      | 2½ hours                  | 100             | 1½ hours                 | 635             |
| D ..      | 2 hours                   | 192             | 50 minutes               | 352             |
| I ..      | 2 hours                   | 350             | 3 hours                  | 400             |
| J ..      | 1 hr. 45 mins.            | 150             | 3 hrs. 10 mins.          | 125             |
| Writer .. | 2 hours                   | 250             | 3 hrs. 10 mins.          | 500             |

Because urine output appeared on the whole to show an increase after the ingestion of cannabis, more detailed study of two cases was done by Dr. Stewart Saunders. These showed a selective sodium and bicarbonate loss. This increase in sodium and bicarbonate is due to a tubular effect, there being no proportionate increase in the filtered load. Inhibition of carbonic anhydrase can also have this effect.

The evidence is sufficiently strong to suggest that further investigation of the diuretic properties of cannabis would be worth while.

The findings are tabulated below:

#### SUBJECT D.

##### *Excretion of Chloride Before and After Cannabis given at End of Period ONE*

| Period | Time (Minutes) | Urine Volume (ml.) | pH   | GFR(Ccr) (ml./min.) | Filtered Load Cl. (m.eq./min.) | Urine Cl. (m.eq./min.) |
|--------|----------------|--------------------|------|---------------------|--------------------------------|------------------------|
| 1 ..   | 124            | 771                | 7·25 | 84·8                | 9·47                           | 0·2395                 |
| 2 ..   | 121            | 660                | 7·8  | 93·2                | 10·21                          | 0·4426                 |
| 3 ..   | 115            | 550                | 8·1  | 92·4                | 10·33                          | 0·3139                 |

##### *Excretion of Sodium:*

|      |     |     |      |      | Na+   | Na+    |
|------|-----|-----|------|------|-------|--------|
| 1 .. | 124 | 771 | 7·25 | 84·8 | 11·66 | 0·1774 |
| 2 .. | 121 | 660 | 7·80 | 93·2 | 13·51 | 0·7810 |
| 3 .. | 115 | 550 | 8·10 | 92·4 | 9·61  | 0·7548 |

##### *Excretion of Potassium:*

|      |     |     |      |      | K+    | K+     |
|------|-----|-----|------|------|-------|--------|
| 1 .. | 124 | 771 | 7·25 | 84·8 | 0·424 | 0·1581 |
| 2 .. | 121 | 660 | 7·80 | 93·2 | 0·475 | 0·1975 |
| 3 .. | 115 | 550 | 8·10 | 92·4 | 0·453 | 0·1148 |

##### *Bicarbonate:*

|      |     |     |      | GFR (ml./min.) | Filtered Load m.mols./min. | Urine Conc. m.mols./min. |
|------|-----|-----|------|----------------|----------------------------|--------------------------|
| 1 .. | 124 | 771 | 7·25 | 84·8           | 2·4334                     | 0·00435                  |
| 2 .. | 121 | 660 | 7·8  | 93·2           | 2·6003                     | 0·168                    |
| 3 .. | 115 | 550 | 8·1  | 92·4           | 2·0882                     | 0·1575                   |

## SUBJECT L.

*Excretion of Chloride Before and After Cannabis given at End of Period TWO*

| Period | Time<br>(Minutes) | Urine<br>Volume<br>(ml.) | pH  | GFR(Ccr)<br>(ml./min.) | Filtered<br>Load Cl.<br>(m.eq./min.) | Urine Cl.<br>(m.eq./min.) |
|--------|-------------------|--------------------------|-----|------------------------|--------------------------------------|---------------------------|
| 1      | .. 60             | 42                       | 5.7 | 80.2                   | 8.52                                 | 0.069                     |
| 2      | .. 60             | 46                       | 6.0 | 83.7                   | 8.89                                 | 0.113                     |
| 3      | .. 60             | 50                       | 6.3 | 78.1                   | 8.83                                 | 0.130                     |
| 4      | .. 60             | 64                       | 6.6 | 89.8                   | 10.12                                | 0.171                     |
| 5      | .. 60             | 62                       |     | 85.4                   | 9.55                                 | 0.150                     |

*Excretion of Sodium:*

|   |    | Na+   | Na+   |
|---|----|-------|-------|
| 1 | .. | 11.15 | 0.076 |
| 2 | .. | 11.63 | 0.105 |
| 3 | .. | 11.30 | 0.128 |
| 4 | .. | 12.30 | 0.207 |
| 5 | .. | 11.61 | 0.212 |

*Excretion of Potassium:*

|   |    | K+     | K+    |
|---|----|--------|-------|
| 1 | .. | 0.2887 | 0.035 |
| 2 | .. | 0.3013 | 0.053 |
| 3 | .. | 0.2812 | 0.036 |
| 4 | .. | 0.3233 | 0.058 |
| 5 | .. | 0.3577 | 0.080 |

*Bicarbonate:*

| 1 | .. | 2.254  | 0.0016 |
|---|----|--------|--------|
| 2 | .. | 2.351  | 0.0032 |
| 3 | .. | 2.280  | 0.0093 |
| 4 | .. | 2.028  | 0.0162 |
| 5 | .. | 2.6937 | 0.0274 |

2. The experiment was repeated on three subjects after an interval of several months. In each case the dose was reduced by one grain. It was striking that they all had the same experience the second time and one could, from their first experience, have predicted with accuracy the pattern of response on the second occasion. Several months had elapsed between the two experiments.

No blood-sugar estimations or electroencephalographic recordings were done on the second occasion and this may have accounted for the only difference observed, which was that the original tachycardia was much reduced and the main abnormality noted in heart rate was that it was more unstable than usual and accelerated rapidly on exertion.

3. The writer took 4 grains of cannabis and remained in bed in the ward until taken home by car in the late afternoon.

Before the cannabis was taken slight frontal headache and some apprehension was experienced. About 90 minutes after the drug had been taken some difficulty in articulation was experienced (this was not objectively demonstrable) and concurrently "I became aware of an astonishing difficulty in recall, so that I could not remember events that had just occurred. This inability of recall seemed to be associated with 'dips' in the level of consciousness when everything seemed rather unreal and hazy and in striking contrast to the periods when I emerged from the dip. It was like emerging from shadow into light. In addition, my concept of time was distorted so that it always seemed later than it really was and the journey down the corridor seemed eternally long.

"My mood change was striking. I experienced some euphoria but to me the really striking thing was detachment. This can be illustrated by the following

examples: I realized that my headache (frontal and occipital) was really quite severe and yet it did not really matter and at the time I compared it to the indifference to pain apparently experienced by patients who have been leucotomized for the pain of inoperable carcinoma; when being wheeled down the corridor in full view of my patients I felt that the situation would normally have embarrassed me and I was struck by my indifference; finally, after I had been taken home and was lying in bed, I could hear my children hilariously swamping the bathroom, which normally never fails to irritate me, and I was astonished at my indifference to it. Physical symptoms were not prominent. I experienced some paraesthesiae of hands and feet, was conscious of coldness and had a bad headache. My pulse rate remained more or less normal unless I exerted myself, when it immediately rose from 80 to 120. I developed slight conjunctival suffusion and had a diuresis. The effect of the drug lasted for 11 hours."

#### 4. *Report of a Subject who took 48 grains of Cannabis*

About three-quarters of an hour after taking the drug the subject felt sleepy, with a heaviness of the eyes and a sense of rotation. About an hour after the drug had been taken he began to laugh uncontrollably and loudly and said that the whole idea of the experiment was killingly funny. For the next hour he laughed a great deal, spoke rapidly and excitedly and became fairly uninhibited in his behaviour, especially towards senior members of the staff whom he called by their first names. He addressed his chief, who had just been elected an F.R.C.P., by his first name and said, "You are very pleased with yourself about that F.R.C.P.—not that it was not richly deserved but really you are so self-satisfied about it." The matron of the hospital was also addressed with great familiarity and the superintendent and other members of the staff were criticized. His report on this aspect reads, "I can, of course, remember speaking a great deal, but time itself pressed on me. I was obsessed with time. There was such a lot to say and so little time and words seemed so insufficient. I remember feeling that I was behaving like a manic—with flight of ideas. I could not stick to a subject and revelled in the sheer pleasure of swinging the conversation round as it suited me. This was a time of intense activity and it all passed like a bright flash. Time and space seemed compressed into one bright minute during which all was gay talk, brilliant jokes and myself the care-free centre of it all."

At this time he experienced a "whirling of objects around a central axis which seemed placed in the middle of the ceiling", and he saw a vivid flash of colours which resembled a modern curtain set against a multi-coloured window. Objects seemed to stand out with "a lively 3-D effect" and the face of one of the observers seemed "exquisite, of very beautiful colour, and a lovely depth that made me want to sculpture his face". He was intensely hungry at this time.

After the first hour the euphoria began to wear off and he complained of various physical discomforts, e.g. intense cold in his feet which felt cold when touched and intense dryness of the mouth and nose. In addition, his hands and feet began to tingle and he complained of weakness of the extremities and several times asked anxiously whether this "peripheral neuritis" would persist. At about this time he wept when a venipuncture was done and said the needle prick was "agony".

He complained of difficulty in focusing his eyes and episodic mistiness of vision.

About three hours after the drug had been taken he became depressed and irritable, looked pale and vomited. He complained of a bitter taste in the



mouth, severe abdominal cramps "like an ileus" and moaned, "What have you done to me?"

He also complained that time was passing terribly slowly.

During the "manic" phase he had a tachycardia of 120 which persisted for  $2\frac{1}{2}$  hours. His pulse rate then came down to 80 and 8 hours later gradually settled to 70.

Five hours after the start of the experiment he looked so wretched and was in such abdominal discomfort that he was put on intravenous dextrose and given 50 mg. of largactil intramuscularly. Despite this he had a poor night and felt irritable and unwell and had periodic abdominal cramps for the next two days.

The report on his electroencephalograms reads: "The initial recording shows a well-marked 8 c.p.s. alpha rhythm posteriorly with irregular fast activity anteriorly and a small amount of anterior alpha. After drug ingestion there is a complete disappearance of the alpha activity and the whole record consists only of low voltage fast activity".

There was no change in blood sugar levels during the first 3 hours of the experiment.

(The abdominal cramps may be accounted for in part by the large amount of liquorice contained in the 48 pills.)

#### *5. Interview with Coloured Male aged 32 Years*

This labourer was completely illiterate and had spent most of his life working with horses in a hawking establishment. He made a good impression, was quick-witted and had an engaging friendliness. He said that he had been smoking dagga regularly (2-3 cigarettes) every night since the age of 15. "Once you smoke it it never lets you go. It makes your mind so that it can never fail. It makes you stronger, makes you laugh a lot and makes you like everybody. It makes me very energetic to my wife so that I even got twins. There is no crime in it—it is only with alcohol that it makes you do wrong things. It is best if you smoke it with other people but if alone you can think you hear the best band playing. Your imagination is so great that you can see someone you have not seen for a long time. But if there are other people with you you don't see or hear anything—you just enjoy yourself. If you smoke it and go to sleep immediately you feel terrible next morning. You must have a little enjoyment and exercise before you sleep and the next morning you feel fine."

He had no intention of giving up the habit and did not think it had harmed him in any way but, on the contrary, that it had enormously increased the savour of life.

#### *Interview with a White Male aged 19 Years*

This youth made a good impression. He had been in steady employment for 4 years, was neatly dressed, courteous and spoke intelligently. He said that he had been introduced to dagga smoking at a party 18 months previously and although he had started the habit as a lark he had found it so pleasant that he had, since that time, regularly smoked two packets of cannabis a night. He always mixed the drug with ordinary tobacco and rolled a cigarette with the mixture. He described the effect as a "sort of light-headedness—like having a few glasses of wine and yet different because it does not make you drunk. Two cigarettes give me a very pleasant feeling for about an hour—I feel like laughing and cracking jokes and somehow one has more courage than normally. Everyone seems to be my friend and it is much more fun to smoke in company than alone. If I am alone I just fall asleep."

He was conscious of tachycardia when smoking, increased desire for food, especially ice-cream because it relieved the dryness of his mouth, and he had also noticed that he passed more urine than usual. He was not interested in alcohol and said that if he were offered alcohol or cannabis he would unhesitatingly choose cannabis. He has gone for several months without it and has not experienced any withdrawal symptoms or any cravings for the drug. The reason why he started smoking again is that he finds the habit pleasant and it does him no harm and he never has a hang-over.

### *Interview with a White Male of 17 Years*

This youth made a poor impression. He left school at 16 having failed to pass Standard 6. He came to the interview because he thought he would be asked to volunteer to smoke some under supervision—"and then you would see how wild I get". He started smoking cannabis one year ago. It was the custom in the gang of about 20 youths of which he was a member. The gang meets about twice a week and are sometimes accompanied by girl friends. They always smoke their cannabis, mixing it with ordinary tobacco, and make a party of the meeting. They take a few bottles of wine and a vast quantity of fish, chips and bread, "because we get terribly hungry". When smoking he feels "very happy, very strong and enjoys talking a lot. I always end up by fighting someone because I feel I can't lose and if I get hurt I don't feel the pain. Once I hurt my leg but did not even know about it until the next day when I saw it was so bad a wound that it had to be stitched."

Occasionally he feels very tranquil after smoking and just wants to lie in the sun and sleep, but usually he becomes restless and either walks aimlessly for miles or picks fights. He has recently acquired a pellet gun and takes it with him when he joins the gang. After smoking several cigarettes he climbs into a tree and takes aim at the other members of the gang. The confusion and fear aroused in them pleases him very much. He said that time had no meaning for him when he was smoking and far from having a hang-over he always felt very relaxed the next day and "could not worry about anything". He emphasized that the gang were not really wild—"we never do anything wrong, like breaking into houses".

### *Interview with a White Male aged 33 Years*

This man claimed that he had smoked cannabis from the age of 14 to 32 but had given up the habit because he had been rescued from this "sin" by a minister of religion. He said that after cessation of the habit he had felt a craving for the drug for 6 months but had not suffered any physical withdrawal effects. (Another addict said that this man was still smoking cannabis.) He gave the impression of being unstable and humourless but had a remarkable capacity for self-observation.

He started off the interview by saying "dagga means women, murder and fight". He seemed to be particularly impressed by its effect as an aphrodisiac and stated that he was obsessed with the desire for women while smoking it. He claimed that his sexual vigour was so enhanced that he had on many occasions slept with 4 to 5 women in one night or had repeated intercourse with the same woman. After smoking he would follow women in the street "white or coloured—pretty or ugly—they all attracted me". If he was unable to strike up an acquaintance with the woman he would seek other women or masturbate. "A man has the energy to go on over and over and after one

time my nature was still high but if I slept even for 30 minutes all desire would leave me." Recently since he began to regard the habit as sinful he would sometimes get a strange feeling while looking at a woman, that "she would seem to change into something strange and horrible, e.g. a stone mountain or a devil". One not infrequent hallucinatory experience was seeing the "devil with long claws and feet looking as though he were going to jump at me and come down on me with his long claws. Then I would cry and pray to God to deliver me from the vice. The next moment I would be laughing madly because I knew it was not really there." He described several occasions when he experienced a marked change in visual perception—"say I was looking at your face, it might change like this—the eyes might start to look Chinese and the nose to broaden until the whole face looked like a mask and then it might make me want to laugh and laugh or if it were a man's face I might go and pick a fight with him. I never felt scared and a fight only ended when I won or was knocked out."

He claimed that his thinking was better when smoking cannabis. "My thoughts get faster and continuous—it is like a verse in your brain as though the devil is talking to me." He quoted a friend of his who when taken to court "always makes a better impression on the magistrate when he has been smoking dagga. He gives the impression of being better educated and cleverer than he really is, because if you think you are clever you seem to be cleverer." Despite the impression of accelerated thought and ideas "when one reads one sticks with one word and can't get any further". He mentioned that talking was particularly enjoyable and for this reason he always sought company when smoking. "Most smokers don't drink much with it—a man can sit the whole night with one small glass of wine in front of him as long as he has his dagga." He said that alcohol and dagga were completely different in their effect. "Dagga is 100 per cent. better—you walk up steady, you think a lot and you enjoy talking." An interesting observation was that he was much more reckless after drinking wine than after smoking cannabis. "Dagga makes you more scared in a way. I would never ride my bicycle or drive a car when I had been smoking because I knew the devil might mislead me and make me have an accident, but when drunk I would not mind doing these things."

He was also struck by the difficulty in estimating time. "If you walk for thirty minutes you think you have been walking for an hour and the same goes for talking."

He had also noted tachycardia and increased appetite, especially for curry and rice, and marked dryness of the mouth even after smoking through water.

He claimed that he could identify a dagga smoker at a glance by the "drooping, narrow, shining eyes".

He denied any hangover after smoking and said that the habit never interfered with his work.\*

#### DISCUSSION

The results show quite a marked individual variation in response to cannabis. This seems to depend more on differences in the basic personality and temperament of the subjects than on difference in dosage. Apart from

\* All the addicts smoked their cannabis and it is difficult to say how much of the drug was absorbed in this way.

The great advantage in smoking rather than ingesting cannabis is that the smoker can regulate the dosage so that with a little practice he can gauge with accuracy the amount that gives him the maximum satisfaction.



one subject who took 48 grains, the range of dosage was not wide, varying between 4-7 grains. In the three subjects in whom the experiment was repeated a very similar clinical picture was obtained on the second occasion despite a reduction of the original dosage by one grain. The impression given by the addicts who were interviewed was that they always reacted in the same way to the drug.

Despite this individual variation one could discern, in all cases, a common basic pattern of response. All subjects experienced a curious disturbance of consciousness, a disorder of time perception, difficulty in immediate recall allied to thought disorder and a change in affect usually in the direction of euphoria. Accompanying these mental changes, the constant physical changes were conjunctival suffusion, paraesthesiae, dryness of the mouth, tachycardia and diuresis.

The disturbance of consciousness is difficult to define. For the first few hours there was in all cases a waxing and waning of contact with reality, or, more correctly, a constriction of the field of awareness. Despite this the capacity for self-observation appeared to be heightened and all subjects responded relevantly if stimulated. Several of them who had no manifest disorder of perception vigorously denied any disturbance of consciousness, maintaining that they were at all times fully aware of their surroundings and the nature and purpose of the experiment. But to the observer there was undoubtedly a definite though often subtle and elusive change in the degree or direction of awareness in all cases.

The disorder of time perception was to all subjects an incredible phenomenon and gave to the experiment a curious, slightly unearthly quality. It always took the same form, i.e. during the first few hours estimated time was always later than actual time—moments of chronological time seemed an eternity. (The only exception to this was the subject who took 48 grains and felt initially that time was passing incredibly quickly while later it dragged with an agonizing slowness.)

There was no clear-cut disturbance of space perception though journeys seemed eternally long. This illusion seemed to be directly related to the time that the journey took.

The change in affect usually took the form of euphoria. The subject who took 48 grains was in a state of sustained hilarity accompanied by great activity for about  $1\frac{1}{2}$  hours. All the other subjects showed a less sustained euphoria, accompanied by excited talking. Although this was to some extent infectious it was clear to the observer that it was out of all proportion to the stimulus. The idea of the experiment would suddenly seem enormously amusing, and oddly enough the subject would often remark on its inappropriateness himself, e.g. in telling some story, with much giggling, he would say that it seemed absurd that it was so funny and yet laughter was irresistible. Occasionally the laughter was bizarrely inappropriate, e.g. one subject laughed as he complained of painful muscle spasms.

Another common mood change was detachment which often alternated with euphoria. It was as though the subject was somehow insulated from everything that was happening to him. This certainly contributed to some extent to the common feeling of double consciousness, i.e. that the subject was himself an observer. Anxiety was not uncommon but seldom gross. It was usually most intense as the drug began to take effect and seemed to be greatest in those subjects who tried to resist the experience. This was well shown by one subject who asked with every indication of intense anxiety for an antidote

to the drug, yet a few minutes later relaxed and said that he could understand people taking the drug for pleasure because once one "gave oneself up" to it it was pleasant.

Some degree of thought disorder was invariably present. In many cases this consisted predominantly of an inability to recall what had just happened so that the subject was often totally unable to sustain a conversation unless prompted about a recent remark by the observer. In some subjects the whole process of thinking seemed broken off abruptly, or they complained of "fragmentation" of thought and described thinking as having no beginning or end and such a tenuous reality that it was continually being shattered by other disconnected pieces of thoughts.

Mayer-Gross *et al.* (1954) stated that as long ago as the mid-nineteenth century Moreau had commented on the dissociation of ideas with cannabis and in 1932 Beringer had described three forms of thought disorder with cannabis. These were:

Fragmentation of perceptive wholes through fragmentation of thought processes. Disturbance of memory by which everything experienced is forgotten at once. Frequent and sudden interruptions of the stream of thought—the gaps only lasting a few seconds. Beringer compared these to epileptic "blanks", or the sudden disruption of the associative links in thinking of schizophrenics.

It is difficult to separate these thought disturbances from one another and they may well be closely interwoven. The sudden blockages of thought and apparent disruption of the pattern of thinking might be no more than consequences of the defect in the power of immediate recall.

The physical changes that occurred in all subjects were also of great interest.

The conjunctival suffusion, uniform and symptomless, was particularly notable. It has been mentioned by many writers and seems to appear at about the same time as the narcotic effect. It persists for many hours and disappears gradually. Chopra and Chopra (1957, p. 20) state that it can persist long after the narcotic effect has disappeared. They also stated that in most addicts a permanent congestion of the transverse ciliary vessels develops. One addict interviewed showed this congestion and his addiction had been of many years standing. A marked proneness to tachycardia on exertion or a sustained sinus tachycardia was shown by all subjects. Even allowing for excitement or tension or muscular activity there appeared to be a definite autonomic imbalance. Dryness of the mouth was universal and marked, almost like an atropine effect, but dilatation of the pupils, if it existed at all, was only slight.

Paraesthesiae in the extremities and peri-oral area was a marked feature in all cases, and in the case who took 48 grains it was accompanied by a subjective feeling of weakness of the extremities.

The more florid symptoms were a disorder of visual perception, the appearance of formed visual images, usually intricate, when the eyes were closed, bizarre disorder of body perception and a marked feeling of dissociation not only of self, so that the subject of the experiment often said he felt as though he were the observer of the experiment, but also of the various functions of self, so that action, volition, thought and effect became chaotically disorganized.

The abnormalities of movement, which in a mild form consisted of periodic contraction of isolated muscle groups, or occasional writhing movements and in a severe form were a continuous medley of movements, are noteworthy because they are so difficult to classify. Beringer observed a great variety of motor anomalies including hyperkinetic and hypokinetic states.

Walton (1938, p. 93) mentions a medical man, Burr, who took cannabis and "suffered a general convulsion which lasted three minutes; he felt well; his speech was not affected. The convulsion resembled an attack of hysteria . . . the convulsions appeared wilful in that he willed to convulse; he knew that he was throwing his arms about, that he was writhing like a snake, acting like a clown, making silly grimaces. But he could not will to do otherwise. He could restrain a convulsion for a few minutes, but soon the will to convulse overcame the will to inhibit." This description is very like the state seen in one subject on two separate occasions, though the use of the term "convulsion" is unfortunate. One is also reminded of the peculiar contortions of the Quakers. In other works there appears to be some neural dissociation but a precise explanation for this extraordinary state eludes one.

Diuresis was suggested by the volume changes in the urine in all subjects. In two cases where the electrolytes were done there was a selective sodium and bicarbonate loss.

The electroencephalographic changes were not specific. Six out of ten showed changes but they remained within the limits of normal. Of these four showed an increase in fast activity and one showed one very short episode of 6 c.p.s. activity in the posterior temporal areas while another developed a moderate amount of bilaterally synchronous 6-7 c.p.s. anterior temporal activity. In the subject who took 48 grains of cannabis the alpha rhythm disappeared completely and the whole record consisted only of low voltage fast activity.

There do not seem to have been many electroencephalographic studies done during cannabis intoxication. Wikler and Lloyd (1945) reported that electroencephalograms during marihuana smoking showed a marked increase in the number and amplitude of the fast waves but these appeared to be of muscular and not nervous origin. Williams gave *ad lib.* doses of pyrahexyl (a synthetic cannabis preparation) to six patients for 26-31 days and stated that during prolonged medication the dominant frequencies were markedly slowed.

The electroencephalographic tracings in this study certainly gave no indication of the site of action of cannabis and at most merely indicated a general cerebral disturbance. It is interesting that Loewe (1950) has described a powerful anti-epileptic effect in all the synthetic cannabinoids that he tested, but at the moment the significance and practical implications of his findings are not clear.

Any attempt to explain the pathogenesis of the symptoms and signs seen in acute cannabis intoxication is purely speculative. One could envisage the process as being a diffuse neuronal change affecting not only the cerebral tissue but also peripheral nerves. The change, being temporary, suggests some subtle and reversible change in neuronal enzyme systems. Rolls and Stafford-Clark (1954) have claimed that one property that all the hallucinogens have in common is their capacity to inhibit the action of amine oxidase. It is tempting to try to fit the conjunctival suffusion into the picture by suggesting that the change is primarily vascular and the suffusion a manifestation of cerebral hyperaemia. It is certainly such a striking and unusual feature that its elucidation may well yield some of the secrets of cannabis pharmacology.

Another possibility is that the principal action of cannabis is on the brain-stem and thalamic structures. The chief argument in favour of this view would be the wave-like effect observed, which might suggest some disturbance of the "alerting" system between the reticular formation and the cortex. A clue



to the temporal disorientation is suggested by the work of Spiegel (1955) who has reported finding it in 23 of 39 cases who underwent thalamotomy for intractable pain. The autonomic changes might also be a result of brainstem disturbance. The apparent involvement of peripheral nerves is not so easy to fit into this theory but anterior horn cells can certainly be profoundly influenced by the reticular formation and there might conceivably be an effect on the afferent nerves.

An attempt to compare the cannabis intoxication with the naturally occurring psychoses leads to immediate difficulties. The lack of any precise diagnostic criteria for schizophrenia is one difficulty and another is the nature of the experimental situation. The mental abnormality seen was not the result of a slow insidious weakening of the ties with reality but an acute disturbance produced in apparently normal well-adjusted young people. Contact with them was maintained throughout the experiment and this fact deserves special emphasis. During the experiment many subjects said that the observer seemed their one link with reality. Solitude and a cutting-off of virtually all sensory input can lead to extraordinary effects as Hebb and his co-workers have shown even without the administration of a drug that has such profound psychic effects. The fact that the observer stayed with the subjects throughout the experiment may well have profoundly modified the results so that in all cases contact with reality was never completely lost, insight in most cases was retained and florid symptoms never became overwhelming.

Despite this there are several features that deserve comment. The subject who took 48 grains behaved very like a manic, with much laughter, talk and flight of ideas, distractibility, lack of inhibition, etc. The other subjects showed more of a schizophrenic picture, especially as regards the apparent fragmentation of thought and the bizarre distortions of perception, notably of body image.

#### CONCLUSION

It is not claimed that any of the results obtained in this study are new in the sense that they have never been described before. They have all been described at one time or another, in the voluminous literature on cannabis. But each age brings some difference in attitude to an age-old problem. At the moment the quest for chemical mechanisms in the psychoses is popular and much can probably be gained from research along these lines.

It is suggested that *Cannabis sativa* may prove a valuable research tool in work of this kind. Its great advantage is its extremely low toxicity and the fact that it can be administered orally. Once its chemistry is fully understood research with it should advance rapidly.

It may well prove to have important therapeutic value as well. There has always been sporadic interest in this aspect because of the euphoria it produces, but so far the wave-like effect has been a drawback. It might be a useful adjunct to psycho-therapy. Although one subject was emphatic about its value in giving him new insight into his basic personality most of the subjects did not emphasize this aspect and all of them, including the subject who took 48 grains, said that they had no difficulty in concealing matters that they did not wish to discuss. Obviously all subjects working together on the staff of a closed institution will have certain reservations about what they are prepared to disclose. This makes the situation different from that in a doctor-patient relationship.

Finally, an interesting sideline was the finding that cannabis is a reasonably

potent oral diuretic which causes a specific sodium bicarbonate loss. With the present search for oral diuretics of this type this may well turn out to have important therapeutic implications.

## SUMMARY

- I. A clinical and metabolic study of acute intoxication with *Cannabis sativa* has been made. Special attention has been paid to its role as a research tool in the model psychoses.
- II. The general history of the drug has been briefly reviewed.
- III. The history of the drug habit in South Africa has been described.
- IV. Experimental work comprised the
  1. Administration of a single oral dose of *Cannabis sativa* to 10 medical volunteers and the observation of
    - (a) Subjective experiences and behaviour;
    - (b) Clinical changes;
    - (c) Special investigations, e.g. blood-sugar estimations, urine output, electroencephalographic tracings.
  2. The administration of a second oral dose of *Cannabis sativa* to 3 of the 10 subjects.
  3. The administration of the drug to the writer.
  4. The administration of an overdose to one subject.
  5. Interviews with four male cannabis addicts.
- V. The implications of the experimental work have been discussed.

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# THE CLINICAL DIFFERENTIATION OF PICK'S DISEASE

By

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## INTRODUCTION

THE aim of this paper is to show how, in our view, the diagnosis of Pick's pre-senile dementia can be made in some cases during life on clinical grounds alone.

We present a description and discussion of three cases examined by us in detail. In all three cases, the diagnosis of Pick's disease was made before death and confirmed at autopsy. During the period these patients were in hospital, we did not make this diagnosis in any other case under our care, and encountered no unexpected cases of Pick's disease among our autopsies.

On the basis of this material we conclude that the pathological changes in some cases of Pick's disease give rise to a fairly distinct clinical picture, which we endeavour to describe.

### *Established Concept of the Disease*

Pick's disease, which was first described over sixty years ago, has never been a well-defined clinical entity. This lack of definition is apparent from the beginning of its historical course, for Pick himself was not concerned with demarcating a particular syndrome: his avowed intention in describing various temporal lobe atrophies was to clarify contemporary concepts of aphasia. The pathological basis of Pick's own cases was varied. He himself considered that those occurring in the older age-groups were part and parcel of the syndrome of senile dementia, but one of his younger patients showed a cerebro-vascular condition secondary to Bright's disease, while another had clinical signs of G.P.I., in addition to cysticercosis of the temporal lobe. A further complication arises from the fact that Pick described lobar atrophies other than temporal, analysing these in terms of a particular resultant organic defect; for instance, occipital lobe atrophy in relation to apperceptive blindness.

Pick's accumulated research on lobar atrophies has been subjected to much sifting out and working over by succeeding writers, as a result of which it has been deduced:

- (1) that circumscribed cerebral atrophy can occur independently of a "senile" cerebral atrophy and that pathological changes in the form of silver-staining plaques and neurofibrillary changes need not be present.
- (2) that such circumscribed cerebral atrophy, involving both grey and white matter, with disappearance and distortion of ganglion-cells (some, on occasion, showing peculiar silver-staining inclusions), is a distinct pathological entity, and belongs more properly to the pre-senile group of degenerative disorders. It is accepted that a minor degree of atherosclerosis may sometimes co-exist without being a factor in the causation of the disease.
- (3) that the sites of greatest predilection are the frontal and temporal lobes.

It is to this type of circumscribed lobar atrophy that the descriptive term Pick's disease has been applied. It may be concluded from such vague general assumptions that the pathological picture is far from uniform, in relation to both localization and histological findings. A perusal of the hundred or more published cases indicates that the clinical picture also lacks uniformity. There is, however, a tendency to group a certain number of symptoms as characteristic of the commonest variant, the fronto-temporal, and this constitutes the usual textbook description of Pick's disease.

#### CASE MATERIAL

In the first case the diagnosis of Pick's disease was made tentatively and was suggested mainly by a consideration of the unique clinical picture, for which it seemed necessary to postulate an atrophying lesion affecting mainly the frontal and temporal lobes. The later two cases showed a striking similarity to the first, and we have felt justified in concluding that all three belong to the same distinct clinical and pathological grouping. (It may be, of course, that we have merely been fortunate in seeing in rapid succession three examples of one particular variant of Pick's disease, and that our conclusions would not be valid for the whole group.)

The clinical features to which we would particularly draw attention, as being distinctive in these cases, may be briefly indicated before the cases themselves are described.

1. Especially prominent was the relative retention, until a late stage in the disease, of our patients' concepts of space and time, concepts regarded as dependent on intact functioning of the parietal lobe. This finding alone appeared to indicate that the lesion originated in the anterior portion of the brain.
2. When suitably examined and observed over a sufficient period, it was found that the faculty of memory was less disturbed in these patients than might appear from their response to formal tests. This finding has been emphasized in previous commentaries, first and notably by Kahn and Thompson (1934), and later by other writers including Nichols and Weigner (1938).
3. The particular type of amnesic aphasia shown by all three patients also appeared to have diagnostic value.
4. More subtle mental changes, less readily attributable to a lesion in this or that cerebral area, yet showing a similar pattern in all three cases and

therefore adding their quota to the demarcation of a particular syndrome, were those relating to personality, affective response, and reaction to testing. The reaction to testing was particularly striking: all three patients showed a marked disinclination to co-operate in formal tests, so much so that assessment of their mental functions had to be made in large measure indirectly by listening to their spontaneous conversation and observing their behaviour.

5. Finally, we were impressed by the occurrence in all our three patients of a physical sign in the form of generalized hyperalgesia. This sign, although mentioned on rare occasions as an incidental finding in clinical descriptions of patients with Pick's disease, has never to our knowledge been regarded as either worthy of comment or of diagnostic importance.

#### *Case 1*

*Summary:* A housewife at the age of 57 began to show personality changes in the form of decreased maternal affection, indolence in the carrying out of domestic tasks (with exaggerated attention to her own welfare) and an obstinate repetition of habitual actions, regardless of their expediency. Over the ensuing four years, aphasic defects became obvious. Her practical performance deteriorated, but she could still find her way about the city, knew the days of the week, and her actions indicated that her memory was not grossly deficient. She complained of generalized pain and winced when any part of her body was touched.

On admission to hospital, some six years after symptoms first appeared, she was still capable of rudimentary conversation and was orientated for space and time. Two years after admission, she sank into a state of hebétude—all initiative lost and speech reduced to a few stereotyped phrases—and this state continued until her death nine months later.

Total duration of illness eight and a half years.

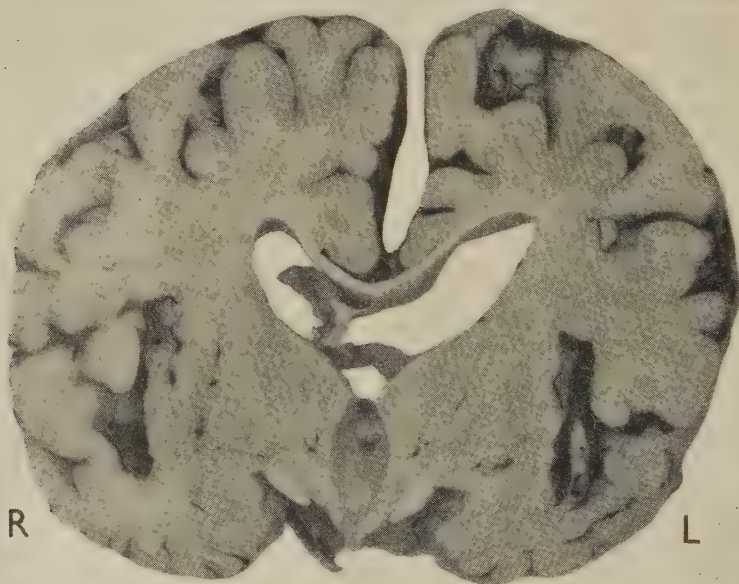


FIG. 1. (*Case 1*)

Coronal section cerebrum showing severe atrophy of both temporal lobes and compensatory hydrocephalus.



Mrs. Elizabeth R., aged 63, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders, on 22 March, 1949.

*Family and Personal History:* Her mother displayed mild mental symptoms for some months before her death in her late seventies. One sister suffered from a right hemiplegia and epilepsy, the alleged sequelae of an injury in infancy, and died aged 40. The patient married, at the age of 24, a tradesman who rose to a managerial position, and had a son and two daughters, a third daughter having died of meningitis in infancy. She had always enjoyed good health and was described as affectionate, hospitable, on occasion obstinate, prone to minor extravagances, meticulous in her domestic arrangements, an excellent cook and dressmaker.

*Phase 1—1943-1947:* The first abnormal sign was the patient's unaccountable and frequently expressed hostility to her elder daughter whom she compared unfavourably to her younger daughter, then absent on war service. She became indolent and slovenly in domestic matters, dusting around objects instead of lifting them, sweeping the refuse from the floor under the mat. She often remarked "I can't be bothered doing that today". She made no effort to accommodate to wartime rationing, and if she could not obtain meat for the midday meal, she told her family "You will have to go to the canteen today". She always prepared the evening meal, but served up the same dish again and again. She lost her former interest in dressmaking, but in 1945, was still able to make a dress for her daughter, albeit the latter had to "stand over her" encouraging her to complete it. She showed increasing querulousness, ceased expressing gratitude and rarely laughed spontaneously, although she smiled in an automatic way when greeting friends. She was never seen to weep. Her son, serving in India, noted that her letters became steadily more egotistical and complaining in content, and more mechanical in style, with repetition of stereotyped phrases. In time, she ceased referring to news contained in his letters to her—"it was as if she never received them". On his return from abroad in 1946, after four years' absence, he noted a marked deterioration in his mother's efficiency. The shirts she laundered for him were too crumpled to wear. She served up the same hastily prepared dish of sausages and potatoes at every meal. When criticism was made, "She wasn't a bit hurt, just took it for granted. Sometimes she contradicted us, but she did it without emotion". In many of her actions she displayed what seemed to the observer wilful obstinacy. One such concerned her habit of scattering crumbs for the birds in the garden. As she now did this with extreme prodigality, she was warned that the food attracted rodents. She paid no heed to this advice. When her husband tactfully fitted up a tray for the food, she ignored it, but if accosted she would walk towards the bird tray, wait till her observer had gone, and then scatter the bread on the ground.

*Phase 2—1947-1949—(year of hospital admission).* Her husband died in 1947 and although she had continued to evince more regard for him than for her family she displayed no emotion at his death. She spent the day of the funeral in a vigorous search for his pipe and tobacco pouch in order to give these to her brother.

From this time onwards her behaviour showed increasing stereotypy. She rose every day at 6.30 a.m., and after giving her family morning tea in bed, she sat about in a dirty dressing-gown reading newspapers—retailing to her family the more horrific events—playing patience or doing cross-word puzzles (she solved these by looking up the answers). She took no part in the preparation of the family evening meal, but cooked her own meal which invariably consisted of fried sausages. She poured the liquid fat into the sink where it congealed, or if forcibly prevented, threw it on the fire undeterred by the resultant blaze. Promptly at 9 p.m., she filled her two hot water bottles and went to bed.

On the same two days of each week, she went out to buy her food, always visiting the same shops and making the same purchase. Every Thursday, she drew her Widow's Pension at the Post Office, where it was noted that she could not always give her husband's Christian name to the clerk. She never lost her way. She could tell the time on the clock and always knew the day, month and year, although, as an aid to memory, she kept a block calendar, tearing off the relevant page each day. Throughout this period she had difficulty in finding the names of persons and objects and employed periphrases to describe what she was trying to name. She showed at one and the same time a decreased ability to understand the conversation of others and an absence of striving to do so.

Physical symptoms appearing during this period were

(a) *Generalized Pain:* She frequently remarked in the morning "I'm sore all over—I

never slept all night with it". When her daughter took her arm or the cat rubbed against her ankles, she cried out as if experiencing unbearable pain. Once when her doctor attempted to estimate her blood pressure, she gave an agonized cry and attempted to strike him. (b) *Somnolence*: She tended to fall asleep at all times of the day and always went to bed at 9 p.m.

*Physical Examination (following admission)*: The patient, a seemingly stolid healthy middle-aged woman, was 5 ft. 4 in. in height and weighed over thirteen stones. B.P. 160/100. Apart from a generalized hyperalgesia which caused her to resent all physical examination, no abnormality was elicited on physical examination or laboratory testing. Blood W.R. negative. C.S.F. findings were likewise negative, and straight X-rays of skull revealed no abnormality. Because of her deficient understanding it was impossible to measure accurately the curious dysaesthesia which she exhibited. Pinprick applied to all areas of the body revealed a seemingly lowered threshold to pain. Venepuncture was only achieved after physical restraint, and lumbar puncture—a procedure in which the patient had no visual threat of the approaching needle—required a general anaesthetic. Conventional pressure such as that utilized in abdominal palpation or the application of a manometer cuff or even the more friendly linkage of her arm with that of a nurse caused immediate wincing and withdrawal, while more severe pressure, e.g., inflation of the manometer cuff, called forth expressions of excruciating pain and motions of self-defence.

*Mental Examination*: Her behaviour showed alternating restlessness when for instance she rummaged in the ward clothes cupboards and scrutinized the name tapes on the various articles, and placid contentment, when she sat quietly playing patience and ostensibly reading magazines. On occasion she played a few simple tunes on the piano. She was able to feed herself and was not incontinent.

Formal testing of her mental faculties was difficult because of her pronounced disinclination to attend. She showed no anxious striving to succeed and frequently pushed test material away, saying, "It's all right, all right", or "I can't be bothered". Her understanding of spoken speech was markedly defective. Even simple questions were not always comprehended, in which case her response was "what do you mean?" or "I don't know". She never confabulated. Her conversation showed stereotypy of content and form. Her vocabulary was restricted, her grammatical constructions simple. On occasion, however, she used elaborate words accurately, e.g., "ridiculous", "evidently". Her frequently reiterated rendering of a conversation between herself and her husband immediately before the latter's death illustrates her asphasic defects. "In November, he just said to me it was his birthday, you see, 64. He just said to me he would not come to me for his dinner, it was Friday, but he said to go into the town just after five, and we would go and have our tea and go to the pictures after that. Coming home, he said, if you and I are spared until I am 65 I will go away into the country and we will let that crew (their family) go wherever they like. I was just hoping that it would be all right, but he died in the November—December. I was very vexed I had lost him." As the above passage illustrates she could convey information relating to numbers with considerable accuracy. Furthermore, she often introduced numerical references which were superfluous or irrelevant to their context, i.e., while elaborating her frequent complaint of her children's alleged impertinence to her, she exclaimed, "you would not think it my house at all," adding the seeming *non sequitur*, "I think it was £2,000 we paid for it" (the house). Her articulation was clear and she never uttered neologisms or distorted particles of words. She described the functions of objects presented to her if unable to name them. She had difficulty with genders and pronouns, at times using the word "son" to refer to her son, husband, brother or father. In relating the deaths of her parents, she said "My son [father] died first, then it was a good long time before my mother died. It just so happened that after he died, I went to him . . . to her, and made him [her] come to my house to stay, but it was just a while before he died . . . before she died, but she was even older than him. I am sure she was bound to be about eighty at that time. My son [father] he was sixty-nine when he died."

She was able to sign her name, but refused to write to dictation. Her reading of printed name cards was erratic, e.g., she read "telephone" and "Bluebell Matches" but refused to read "apples". She refused to approximate name cards to their appropriate objects. Her handling of illustrated papers suggested that she understood some part of their content, but she never commented on them. She could count concrete objects laid before her, but would not essay simple mental arithmetic.

She could tell the time on a clock face and assess the time of day. At first she could give the day and date of the month correctly, but soon lost this ability. Recognition of the months of the year was retained for a longer period, and when she was presented at a clinical meeting on 23 June—she said the month was “June” adding “this will be near the end of it”. When she could be persuaded to do so, she copied simple diagrams accurately. It was noted that she placed her cards correctly when playing patience. She never lost her way in a hospital block of many wards and corridors, but she was not aware of the name of the building nor of its function. She distinguished her right hand from her left and showed no dressing apraxia.

She recognized but was unable to name the members of her own family. She referred to them as “my son and two daughters and the lassie who has just got here you see”—this last phase categorizing her daughter-in-law who had lived abroad before her marriage. Her conversation indicated that she recollected events of strong personal significance in the present and recent past, i.e., her domestic activities, the activities of her children in so far as they impinged on her own, the circumstances of her son's second marriage and of her husband's death. She tended to dwell more on the recent than on the remote past, but if distant events were recalled to her, e.g., the deaths of her parents, she could elaborate the relevant details. She seemed aware of the chronological sequence of events, which she recalled spontaneously or by direction. Temporal association could act as a stimulus to recall. For example, in a conversation about her son's second wife, she was asked “Has she any children?” and she replied, “No, it was only in December (i.e., four months earlier) that he married her”, adding, “It was the year before that that my man was dead”. Here the stimulus word was December since her husband had in fact died the December before. Her total response to the foregoing question furthermore proved the retention of some degree of reasoning ability. She had no recollection of events outwith the personal and concrete. She showed some degree of insight in that she often ejaculated “I have got so stupid I cannot mind (*anglice*—remember) things at all”, but she had no realization of her total situation.

*Subsequent Course:* Within a year, the generalized hyperalgesia had ceased to be evident. She developed a gorilla gait with bowed trunk and limply hanging arms. Her vocabulary became progressively more impoverished. Finally, with no intervening phase of dysarthria or paraphasia, she passed into a state of relative mutism, repeating infrequently a few phrases culled from her conversation with her husband (quoted above). Mental and physical activities coincidentally declined, and during the last nine months of life she lay in bed inattentive, but was rarely incontinent.

She died suddenly on 30 December, 1951.

*Necropsy Findings:* Both main branches of the pulmonary artery were occluded by partially coiled ante-mortem thrombus which had had its origin in the left femoral vein. There was early, incomplete infarction of both lungs. The coronary arteries and aorta showed moderately severe atheroma.

THE BRAIN showed slight generalized atrophy of the whole of both cerebral hemispheres, but in addition there was a lobar atrophy of both temporal lobes and of the left frontal lobe. This wasting was most marked in the left temporal lobe where the anterior two-thirds of the superior, middle and inferior temporal gyri and the anterior 2.5 cms. of the hippocampal gyrus were considerably shrunken and firmer than normal. The fusiform gyrus was intact. In the right temporal lobe the atrophy was less marked and involved only the anterior one-third of the middle and inferior temporal and fusiform gyri. The left frontal atrophy was confined to the anterior two-thirds of the lobe. The leptomeninges covering these affected lobes were thickened and slightly wrinkled, but elsewhere over the surface of the hemispheres they appeared healthy. The arteries at the base of the brain showed patchy atheroma. No abnormality of the cerebellum or brainstem was seen.

Section of the brain confirmed the lobar atrophy and showed that in the left temporal lobe the gyri were reduced to thin lamellae. The anterior part of each insula shared in this atrophy. No obvious involvement of the basal ganglia could be seen. There was a marked compensatory dilatation of both lateral ventricles which was most marked in the left anterior and posterior horns. The third ventricle too was dilated.

*Microscopic Observations:* In the left temporal lobe there was widespread atrophy of both cortex and convolitional white matter. The neuronal loss affected all layers of the cortex. Surviving nerve cells appeared atrophic and degenerate but there was no ballooning of nerve cells; and no argyrophilic inclusions, tangles or senile plaques



were seen. There was evidence of loss of myelin from both cortex and white matter and in response to this a quite marked gliosis had occurred. The leptomeninges showed very slight fibrous thickening.

The changes in the right temporal lobe and in the left frontal lobe were similar to those in the left temporal lobe but were less severe.

Sections examined from parietal and occipital lobes showed simply the mild changes expected to accompany moderately severe, generalized cerebral atherosclerosis.

In the basal ganglia there were a few small glial scars related to the vascular disease. In the midbrain too there was evidence of atherosclerosis but there was no demyelination of frontopontile or temporopontile tracts. A small quantity of free melanin pigment indicated minimal nerve cell loss from the substantia nigra.

In all sections there was evidence of moderately severe atherosclerosis. The arterioles appeared healthy.

### Case 2

*Summary:* At the age of 50, an unmarried female school teacher was observed to show increasing egocentricity, lack of inhibition and narrowing and rigidity of her interests and activities. Five years later, aphasic defects became obvious, her practical performance deteriorated, but memory and orientation were not notably impaired and she was able to live alone without domestic help until her admission to hospital twelve years after the first appearance of personality changes. Examination revealed a generalized hyperalgesia. Death occurred two years after admission, being preceded by a terminal phase of mutism and immobility.

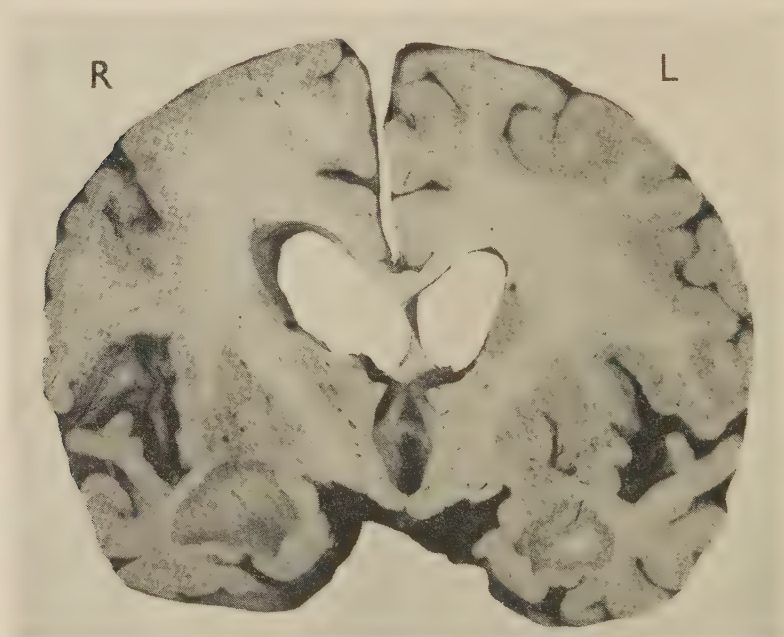


FIG. 2. (Case 2)

Coronal section cerebrum showing severe symmetrical atrophy especially of temporal lobes. Also compensatory hydrocephalus.

Miss S. V. P., aged 62, a retired teacher of needlework, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on 26 September, 1950.

*Family History:* The paternal grandmother and a paternal aunt suffered from a memory defect for a few years prior to their deaths in the ninth decade of life, and another paternal aunt had a child who was a mongolian idiot. There was no other relevant family history.

*Previous History and Personality:* She had no nervous traits as a child. At the age of 19, she became highly-strung and excessively concerned for her own personal safety. There were periods of a few days when she lay in bed trembling. From these symptoms, she recovered spontaneously when she was 24. At 27, she gained a teaching diploma in needlework, then taught in primary schools, and retained her last post from the age of 38 until she retired at 60. She had lived alone since 1941.

She was described as being very variable in temperament, but, on the whole, popular, competent and extraverted.

*Medical History:* Radium menopause at 32, followed by flushings and severe headaches until the onset of her mental illness at 50. At 50, she was struck on the right eye and nose with a shuttlecock, and the region was, for a time, swollen. At 60, she fell and struck her head, but did not lose consciousness.

*Present Illness:*

(a) *Phase 1—age 50–57.* Her relatives, who dated her illness from the badminton accident, first observed that, instead of wearing a dressing over the injured part of her face, she carried an umbrella to protect it from the sun. She became progressively more self-centred in her outlook and her activities became more stereotyped. She developed a rather silly, flat laugh. Her memory showed occasional lapses. For example, she forgot entirely about a letter she had sent to her relatives. Towards the end of this period she was occasionally unable to recall the names of things she used in her work, such as scissors and thimbles.

(b) *Phase 2—age 57–62.* During this period, her speech showed the greatest decline. She increasingly forgot the names of people and things, but was able to converse by substituting generic terms such as “thing”, “man”, “woman”, or different but related words such as “school” for any building, “letter” for “key”, “bread” for “cakes”, “water” for “ink”. Sometimes she transposed genders and family relationships. She understood progressively less of what was said to her. She gave up reading newspapers and writing letters, and communicated entirely by telephone. (She was thus able to manipulate the dialling system.) She lost her ability to calculate, required help with her accounts, and would hand banknotes trustingly to tram conductors and shop assistants. She remembered recent personal events with only occasional minor lapses, but became completely ignorant of current affairs in the outside world. She perseverated in her speech, and would repeat the same ideas over and over again. She was able to identify by sight her friends, places in the neighbourhood, and playing cards. She remembered important dates and anniversaries, but, at the beginning of Summer Time in the year of admission, arrived at church an hour late. Her spatial orientation remained good with only occasional lapses. Latterly she did not usually identify her friends and relatives at once, unless she had reason to expect to meet them, when she would greet them without hesitation. Sometimes, however, she revealed by her conversation that she was confusing her hearer’s identity, e.g., she mistook her niece for her aunt, and the minister for her brother. Not normally tidy, she became obsessively so. Nevertheless, her standard of needlework and her housework deteriorated. She would put sugar on ham and eggs and tea in the soup. She formed the habit of lifting the kettle from the fire with a large cloth which frequently caught alight, and she persisted in this despite the repeated warnings of her friends. She could not learn new procedures, but managed to do her routine shopping. Her dress became slovenly and dirty. She fell asleep frequently and slept soundly. She made no attempt to understand anything not directly related to her own narrow objectives, but understood fairly well the processes of shopping and obtaining her pension. She developed a habit of talking loudly in public about her personal affairs to anyone who would listen. She bought bizarre articles, for instance, a bright red coat for herself and a handbag for her nephew on his marriage. Obstinaey, suspicion and caution became more and more prominent, and she would lock the door of her living room, as well as her front door, before settling down for her weekly game of rummy with her friends. At public meetings, e.g., in Church or at school, she became readily excited and irritable. She knew when to seek help with her letters and accounts, and frequently remarked: “Och! I’m going daft.” She remained active and was able to look after herself although living alone, until only six weeks before admission.

*Examination on Admission:* She was short, stocky and grey-haired, with a rubicund, cheerful countenance. Her personal habits were of a good level. Although she took no

part in the work of the ward, she attended Occupational Therapy Class. She showed pressure of speech and perseveration. Her affect was one of mild euphoria, characterized by a frequent rather silly laugh. This would be interrupted by a fleeting irritability. Her conversation was a series of random and reiterated explanations of her personal affairs, with interpolated comments on where she slept, when she expected her brother's visits, etc. By far her most striking disability lay in the sphere of speech and it was of such degree that only close attention and practice enabled the examiner to converse with her at all, although her articulation was quite clear. In expressive speech, she was able to use adjectives and verbs, e.g., "particular" and "retire", with more accuracy and facility than nouns and pronouns. She was either unable to find words at all, or used wrong but related or generic terms. "Glasses" or "tea" sometimes meant "money", "school" meant "house". She frequently used "man" for "woman", "she" for "he", and "father" for "brother". When tested with simple objects, she usually refused to name them at all. If told the name, she usually repeated it, but was unable to name it again a few seconds later. Her errors were inconstant, she did not have fixed words which "stood for" others, and she sometimes used the correct words. Similarly, she understood the spoken word erratically and with difficulty. A sample of her speech is as follows:

"I'm S. V. P. and I live along at the school (at my home) but here I've been writing something over there (embroidering a cloth at the Occupational Therapy Class) . . . Yesterday I was doing that thing (embroidering that cloth) . . . I want to wash that thing (the cloth). I want to have it done. You see my brother's coming tomorrow and I might go away. I live alone at my own house which is a great big place, up and down (upstairs and down) with a garden. I'll have to go and do that letter (embroidery)." She refused to read continuous print, but if a page were handed to her upside down she invariably turned it the correct way. When encouraged to spell out words, she seldom named the letters correctly, and when given the alphabet in jumbled order, she read it out in the correct order, pointing to each successive letter as if she were reading it correctly. She could write her name, but very inaccurately. She quickly lost interest in testing, but never showed a catastrophic response to failure. Instead she would rationalize, saying, "I live alone and I never bothered; I need my glasses; etc.", or admit frankly "I don't remember the names of things", or look crestfallen and push the test away with the phrase: "Och! I'm daft." She never confabulated. She was surprisingly well orientated. She quickly knew her way accurately about the ward. Two weeks after admission, she took two doctors, without hesitation, by what was, for her, an unusual tram route, and thereafter through a complex maze of suburban streets, to her home. She pointed out places on the way, and, although she could not name them, usually showed that she understood what they were. She once referred to "being put away here". Two weeks after admission, she referred to being here two weeks. She frequently indicated that she had left school two years before, which was correct. She referred correctly, but in her aphasic way, to events of the previous day, and was aware when Saturday (her brother's day for visiting) came round. She regularly went to the table at the correct times, in anticipation of meals. She knew her own identity, recognized the doctors, her visitors, and numerous neighbours during her visit home, but the only names she ever mentioned were her own, her brother's and her niece's. Her memory was difficult to test, and her response was erratic: she remembered events in her past life, recent events in the ward, and her visit home, but on one occasion she carefully put her spectacles and handkerchief under a pillow, and immediately proceeded to look for them elsewhere. Hearing and vision were obviously not grossly impaired. She refused to name colours, and, in her embroidery, consistently failed to change colours when this was obviously required. When shown various objects and pictures, she never named them, but often picked out minor details or indicated one of their uses; e.g., when shown a watch with the hands set at eight o'clock, she said, "I need my glasses. I can't see it. I live alone. It's eight o'clock, isn't it?" She could count as far as twenty, identify the numbers of tram cars, and reckon days and weeks, but was unable to do other simple calculations. When shown half-a-crown, she said "Oh yes, that's two, is it, or is it two and a half?" She could construct a triangle and make a poor copy of a five-pointed star with matches. Her embroidery (a professional skill) was slow and of a very poor standard, but she was able to follow the pattern correctly. She could put on her clothes and gloves correctly, but if the examiner pointed to his own thumb, she would grasp her little finger. Her social sense and judgment were impaired, so that for the most part she accepted uncritically her position in hospital and would think nothing of announcing publicly her intention of visiting the W.C.



*Physical Examination:* Neurological examination showed a slight tremor of the left hand, tigroid retinae and a well-marked hyperalgesia to painful stimuli over the whole skin surface. B.P. 150/110. Apart from moderate obesity, no other abnormality was found on routine physical examination. Blood W.R. was negative. Lumbar puncture provided a clear, colourless fluid under 60 mm. of pressure, with a free rise and fall under jugular compression to 150 mm.: 2 cells per cu. mm.; 50 mgm. Protein per 100 mil., a trace of globulin; 66 mgm. Sugar per 100 mil.; negative W.R.; and colloidal gold curve 0000000000. Straight X-rays of skull revealed no abnormality. E.E.G. was somewhat spoiled by movement artefacts, but showed no definite abnormality.

*Progress:* For the first eight months, no major change in her mental condition occurred. Her right shoulder became lower, so that her trunk was bent over sideways, and her steps became short and shuffling, with a side-to-side rolling gait. During this period she frequently referred to the expedition to her home. During the next six months she showed a marked deterioration in all spheres and at the end of this time she was completely bed-ridden. All proprioceptive reflexes were exaggerated, she had bilateral ankle-clonus and an occasional coarse rhythmical munching movement of the jaws, and a perpetual fingering of the mouth and nose. She was able to feed but not dress herself, was regularly incontinent of urine and also occasionally of faeces. She showed little interest in her surroundings and was unable to co-operate in any examination. Perseveration became very marked, and her aphasia prevented almost all communication, although articulation was hardly impaired at all. She was able to perform only very familiar actions. At the end of the next twelve months, she had paresis of both limbs on the right side and a generalized muscular rigidity of Parkinsonian type. She was now quite mute. Babinski's, Oppenheim's and Meyer's signs were all negative. On 21 December, 1952, she developed crops of blisters. She became comatose on 30 December, 1952, and died on 31 December, 1952.

*Necropsy Findings:* There were multiple bedsores. There was a well-established bronchopneumonic consolidation of both lungs.

THE BRAIN showed moderately severe generalized atrophy with a severe lobar atrophy of both frontal and both temporal lobes. The leptomeninges were not thickened. The vessels over the surfaces of the hemispheres were healthy and the arteries at the base of the brain showed only a slight diffuse thickening of their walls and no evidence of atheroma. No abnormality of midbrain, pons or medulla or cerebellum was seen.

Serial coronal sectioning of the hemispheres showed that the wasting was most marked in the left temporal lobe, and that although the superior, middle and inferior temporal gyri and fusiform gyri were grossly shrunken, the hippocampal gyrus was intact. In the right temporal lobe the inferior temporal and fusiform gyri were severely affected but the superior and middle temporal gyri were also atrophied. The wasting of both frontal lobes was particularly well marked on the orbital surfaces. The anterior half of each insula was wasted and the caudate nuclei appeared slightly smaller than usual. There was marked compensatory dilatation of both lateral ventricles which was most marked in the body and temporal horn on the left side. The third ventricle shared in the dilatation.

*Microscopic Observations:* In the severely wasted temporal gyri there was a profound loss of nerve cells from the cortex and surviving cells were degenerate and contained a large amount of lipofuscin pigment. There were no ballooned cells and silver stains failed to demonstrate intra-cytoplasmic inclusions, tangles or senile plaques. The convolutional white matter was shrunken and there was considerable thinning of myelin. This atrophy was associated with marked astrocytic increase and glial formation but there was no microglial activity. The leptomeninges showed slight fibrous thickening with histiocytic infiltration of the subarachnoid space. In the less severely wasted temporal gyri the changes were similar but less marked.

The atrophy in the frontal lobes affected both grey and white matter. The cortex was narrower than usual and the nerve cell loss was more marked in the outer laminae so that the pyramidal cells appeared more superficial than usual. There were no ballooned cells or argyrophilic inclusions.

No significant abnormality of the occipital lobes could be seen.

The basal ganglia appeared normal and showed no obvious nerve cell loss or gliosis. The section from the midbrain showed no appreciable reduction in the number of cells in the substantia nigra but the presence of histiocytes containing melanin

indicated that degeneration of occasional cells had occurred. There was no evidence of demyelination in the cerebral peduncles.

In all sections the arteries appeared healthy but some of the arterioles showed slight hyaline thickening of their walls.

### Case 3

*Summary:* At the age of 54, a married woman formerly noted for unusual energy and social poise became lazy, quarrelsome and tactless. Five years later, she complained of generalized bodily pain, and coincidentally was observed to have difficulty in finding words and performing complex tasks. From this time onwards her vocabulary became more impoverished, her interests more restricted and her programme of domestic tasks simpler and more stereotyped. Her topographical sense remained relatively intact. In her unaccompanied expeditions to shops, the cinema and her club, she was observed to adhere to a rigid timetable. On admission to hospital, nine years after the onset of symptoms, it was noted that she winced when pressure was applied to any part of her body. After a year, she slowly sank into a state of inertia and mutism which continued until her death three years and four months from the date of admission.

The duration of the illness was approximately twelve years.

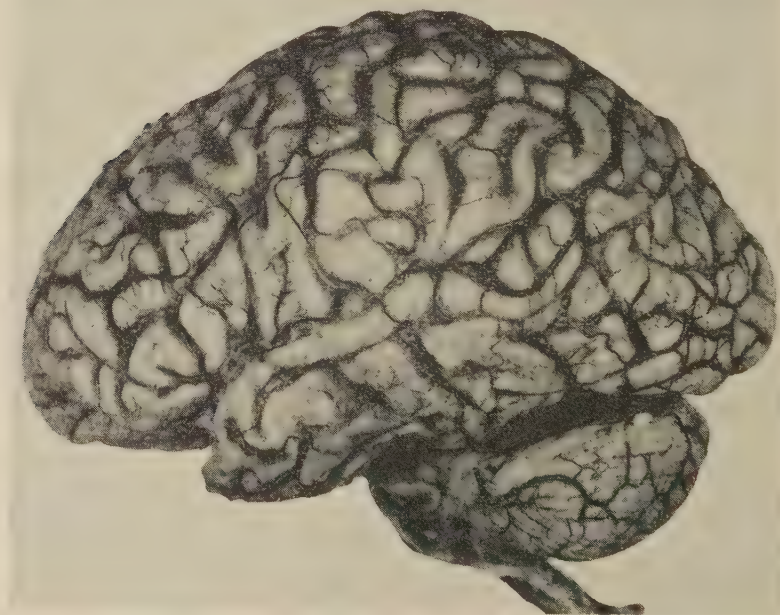


FIG. 3. (Case 3)

Lateral aspect of brain showing severe atrophy frontal and temporal lobes.

Mrs. Edith M. R., a housewife, aet. 63, was admitted to the Royal Edinburgh Hospital for Mental and Nervous Disorders on 14 April, 1952.

*Previous History:* Family history was negative, apart from a record of explosive temper in the maternal line. In a motor accident at the age of 21, the patient was thrown against the windscreen sustaining a deep laceration between her eyebrows which left a permanent scar. While in Salonika during the 1914-18 war, she suffered from recurrent malaria. Following her marriage in 1920, she spent the next twenty-two years in Malaya, where she enjoyed excellent health. She had a family of two sons and a daughter, of whom one son was killed in flying operations in 1940. Her husband described her as quick-tempered, somewhat obstinate "but always amenable to reason". Possessed of abundant energy and initiative, she was a talented singer, a good dancer, an expert bridge player, an amusing conversationalist and led a full and busy social life.

*History of Illness:**Phase 1—? 1943-1948.*

(a) *Personality Changes:* Unusual wartime circumstances made it difficult to date the onset. In 1942, the patient along with her daughter, aet. 12, was evacuated by sea from Malaya and after spending some time in South Africa arrived in Scotland in late 1943. Her sister, who had last seen her on leave four years earlier, noted a definite change in her personality. She was lazy and unmethodical, egocentric and querulous, always complaining that "no one seemed to appreciate her". She was incredibly stupid in the handling of her daughter, whom she had pushed into a state of open rebellion. The two years she spent with her sister were rendered difficult for the latter because of the patient's constant squabbles with her daughter and her tactless remarks to friends. On her husband's return from Malaya in 1945, she moved to a house of her own, but her attempts to establish her accustomed social life ended in failure. Friends ceased attending her dinners and bridge parties, and it was later learned that they had been embarrassed by her recounting of intimate details and her constant derogatory references to her husband and family.

(b) *Phase 2—1948-1952 (Admission to hospital):* She complained of generalized bodily pain and was treated for rheumatism at various clinics without relief. Her husband now noted that she had difficulty in recognizing acquaintances, in naming common objects and in carrying out complex domestic tasks—for instance, she was seen to refer to a cookery book when concocting well-known recipes. Somewhat later she began to cheat at bridge and on a shopping expedition stole a box of chocolates from a shop counter, showing no concern at the subsequent expostulations. (During the next four years, she was apprehended five times for similar blatant shop-lifting.) In 1951, it was discovered that she had withdrawn £500 from the bank, which she had spent in addition to her considerable housekeeping allowance. The bank manager related an incident when he had refused to cash her cheque, explaining to her that her account was overdrawn. She listened and appeared to understand, but immediately his back was turned, presented her cheque again at another counter where it was cashed by an unsuspecting teller. After this incident, her husband paid all the household accounts and she was allocated a small weekly allowance, which she often squandered in a single purchase of cakes or jig-saw puzzles. Her vocabulary became increasingly restricted but her conversation continued voluble, being liberally interlarded with stereotyped phrases. In 1950, her letters were reported as unintelligible by their recipients, and her husband persuaded her to write at his dictation. She ceased opening letters addressed to her, but continued to borrow and read library books. Her domestic efficiency now showed still further decline. She drew together rents in household linen instead of darning them: she used a simple floor sweeper instead of her electric vacuum cleaner. When preparing meals, she utilized tinned soups and ready-made puddings. As the main dish she invariably served fried mince and sausages. She kept the soup hot by placing it in plates in the oven, and could not be dissuaded from this practice when it was repeatedly pointed out to her that the resultant pellicle formation rendered the soup unpalatable. She adhered to a rigid time-table in performing her household tasks. A like rigidity was evident in her programme of social activities—visits to friends, expeditions to shops, the cinema and her club being relegated to specified days of each week. At her club, she invariably ordered two whiskies and soda and never exceeded this number. She had no difficulty in route finding, knew the destinations of trams and buses and negotiated traffic without mishap. Every Saturday she went with her husband to watch her favourite football team, and her running commentary indicated that she followed the moves in the game. She enjoyed variety shows but no longer understood a straight play. She could assemble 200 piece jig-saw puzzles and could take part in simple games like three-handed bridge and ludo. She knew the time of day, could compute periods of time and remembered family anniversaries. Although her memory for events and people was capricious, and she frequently mislaid articles, her conduct and conversation indicated that she retained day to day events of personal significance. She rarely referred to events in the past. Her general mood was one of euphoria, unless her comfort was menaced or her wishes disregarded. Flashes of irritability and explosive temper would then occur. She had no social inhibitions and would complain loudly of anybody or anything arousing her displeasure.

*Physical Symptom of Pain:* Reports on the patient's attendances at a Rheumatic Diseases Clinic in 1948-50 describe her complaint of "aching pains all over, mostly



affecting the shoulders and neck" and state that all treatment proved ineffective. It was recorded on one occasion that "her response to any sort of examination is grossly exaggerated". In 1950, she was seen by a psychiatrist (Dr. A. B. Hegarty) and later by a neurologist (Dr. K. Hermann), both of whom demonstrated organic intellectual deterioration which they considered was based on either Alzheimer's disease or Pick's disease. The neurological report records that the patient showed "marked spontaneous pain in the right limbs with no restriction of passive joint movement and no tenderness of the muscles" and stresses her lack of co-operation in the various examination procedures, e.g., sensory examination. On the physical side, no definite neurological abnormalities were elicited.

*Physical Examination:* The patient was an obese, well-preserved woman of middle-age. B.P. 143/78. No abnormality was found on clinical examination apart from a generalized hyperalgesia. Pinprick or pressure applied to all areas of the body evoked an exaggerated response. This response showed some day to day fluctuation in that it ranged from mere facial expressions of discomfort to vocal expressions of pain accompanied by gestures of withdrawal. Blood W.R. was negative. Lumbar puncture (which did not require, as in Case 1, a general anaesthetic) provided a clear colourless fluid under normal pressure: 6 cells per cu. mm.; 48 mgs. Protein per 100 mil.; 70 mgs. Sugar; 760 mgs. Chloride; Negative W.R. and Colloidal Gold Curve 0011100000.

*E.E.G. Findings:* An E.E.G. record taken on 3.12.53 showed only symmetrical stable alpha rhythm (8-10 c/sec.) and traces of low voltage 4-7 c/sec. activity in the parietal, occipital and temporal areas.

No recognizable activity was recorded from frontal areas.

A second routine record taken on 27.5.54 showed no new features. Further recording after the administration of 3 grs. "Seconal" showed symmetrical fast activity with a predominantly frontal distribution due to the barbiturate, and symmetrical sleep changes and aroused responses.

*Mental Examination:* The patient appeared most contented when allowed to remain in bed. There she occupied herself in assembling one or other of her 200-piece jig saw puzzles, in whistling a tune, or merely in following with her eyes the actions of persons in her vicinity. She required coercion to get up, but having done so carried through an elaborate toilet ritual, which included the application of cosmetics. She tended to be restless when ambulant, exploring corridors and side rooms and demanding of members of the staff (whom she seemed able to differentiate from patients) that she be allowed to go home. On occasions, she sat down at the piano and played a few simple melodies, or standing upright accurately hummed a tune, the while keeping time by slapping her thighs or tapping her feet. She showed a lack of social inhibition in that she would undress and talk loudly about her excretory functions when strangers were in the ward.

During interview, she kept up a constant flow of conversation, showing no defect of articulation or syntax. Despite an obvious gross reduction in her vocabulary—particularly in respect of substantives—her conversation showed no hesitation, since she utilized periphrases to convey her meaning, and interpolated a number of constantly recurring stereotyped phrases. Her conversation was also liberally sprinkled with superlatives and terms of endearment—"I think it's really wonderful, marvellous, to be doing this thing, darling. No, I can't remember words at all, but I'm really disgusted because I used to. I'm not joking, but I'm really disgusted. Yes, it's awfully bonny, but I can't remember words." While obviously unable to comprehend abstract terms and ideas she understood the gist of most of the simple questions addressed to her and a knowledge of her previous life history enabled her examiners to understand what her periphrastic sentences were intended to convey. Her attention was not always easy to obtain and testing of her various faculties had to be carried out mainly through the medium of conversation. Shown simple objects she would wave them away with some such remark as "It's awfully bonny, I cannot remember words", but might follow this up by a further comment which showed that she had a clear idea of the function of the object. Shown a pipe, she said, "Oh, my husband does that", shown a florin, she exclaimed "you are lucky, I haven't any money", and when the coin was presented later, she said "that's a two" (shillings). It was noticed that although she failed in nomenclature, she often gave numbers correctly, e.g., shown a picture of twelve marbles, she counted them accurately but was unable to name them; shown a watch, she said swiftly, "eight" which was the time registered on the watch face. She tended to confuse genders and relationships. Asked about her brother, she replied by referring to her sons. "Well,

there was two, and funnily enough the older one was gone (killed) and really it was very bad. *She* was gone, it's really disgusting because he was awfully bonny and really very tall and I think 18 (actual age of elder son when killed in action). It was really very bad luck."

She read a series of name cards with only one or two mis-pronouncements. (She handled the cards expertly, putting each one at the back of the pack after she had read out the printed word.) She refused to read a passage from a book, and similarly refused to write to dictation. On one occasion she agreed to write her name. She wrote "Edith" then paused and enquired "my husband's one, I've forgotten?" On being told her surname, she wrote it accurately.

She refused to draw or copy designs but her ability to complete patterns was illustrated in her assembly of jig-saw puzzles. She first selected pieces of the same colour, then separated out the straight-sided pieces which formed the outline, after which she set to work to build up the picture. Her topographical sense remained relatively intact in that she never lost her way in ward block of many rooms and corridors. An attempt to assess her topographical sense outwith hospital was less successful than a similar attempt with Case 2. It was not feasible to take her to her home, so she was taken to her club in a motor car by a different route from that of her former approach. She failed to recognize landmarks or the club building, but once inside she found her way by scrutinizing the printed signs. She conversed about the type of meals and drinks she used to have in the club and said "my husband and I are always there on Friday, Saturday and sometimes Wednesday" (which was correct). She behaved normally when crossing streets and on one occasion seized hold of one of her escorts when he stepped off the kerb in front of an oncoming vehicle.

In conversation, she used the adverbs of place, e.g., "up" and "down" correctly. Referring to her house, she said "There are six of them" (a terrace of six houses): "they are all lovely, big, proper upstairs and downstairs. I do it awful nice. Get lunch for Sandy and my husband, then I wash the kitchen all over and when finished and all the things, I go upstairs and tidy, put on a proper thing and do my hair."

She knew the days of the week but not the month or year. She could assess the time of day and compute the number of days since her husband's last visit. She could assess in weeks the duration of her stay in hospital, describing this as "more than three", or "more than ten" and so on until twelve weeks were reached, after which her response became erratic.

Her memory could only be assessed from her behaviour and conversation. She was able to find her own clothes, although she did not always hang them in the same place. She spoke of her escorted visit to her club a month after it had taken place. While she had obvious memory impairment yet she was able to supply many details about her family, her house and her social interests. It was notable that she frequently interpolated numbers into her conversation, as if to compensate for her verbal impoverishment. "Funnily enough on Saturday we go to the Empire at 8.40. I love it, I'm not joking. But on Sunday at 6.30, the nice place, the proper thing—different ones." (This last sentence referred to her husband's habit of taking her to a different church every Sunday evening.) Again, in anticipating her husband's visit, she invariably mentioned both the day and hour of his arrival—"my husband will be coming on Saturday at 2.30 or 3". She often spoke of her life in Malaya, of her evacuation therefrom and temporary separation from her husband—"Funnily enough I went out and went to that place (South Africa). Lucky because my husband did things for all the different ones, for all those other men. It was bad luck. I went away down (to South Africa). Then I went away here. He (her husband) was coming along. It was very lucky." She rarely referred to the remote past or to her childhood.

Her mood was euphoric with episodic brief outbursts of irritation during which she might attempt to slap persons in her vicinity. Apart from her reiteration of her inability to remember words, she made no remark to indicate her realization of her situation.

*Subsequent Course:* After a year, she sank into a state of relative inertia and immobility, responding to greeting by mumbling a few stereotyped phrases, i.e., "I'm really disgusted, I never realized. Along in that place, dear, with all the proper bonny things." The generalized hyperalgesia was no longer apparent. Within eighteen months of admission, she was bedridden and doubly incontinent. She now stuttered when enunciating her few stereotyped phrases. In the last six months of life she was completely mute. She exhibited a mask-like facies, a waxy rigidity of all limbs and a grasp reflex.

Death occurred on 17 August, 1956, following bronchopneumonia.

*Necropsy Findings:* The lungs showed areas of bronchopneumonic consolidation. There were multiple bedsores about the sacrum, buttocks and heels.

THE BRAIN weighed 1,140 gms. There was severe, bilaterally symmetrical atrophy of both temporal lobes affecting particularly the middle and inferior temporal gyri and the fusiform gyri, but also the superior temporal and hippocampal gyri. The wasted gyri were abnormally firm in consistency, showed slight yellowish brown discoloration and sharp angulations in place of the usual rounded contours. The intervening sulci were widened and deepened and cerebrospinal fluid had accumulated deep to the thickened arachnoid bridging these gyri. There was also a symmetrical, but only moderately severe atrophy of both frontal lobes and slight atrophy of both parietal and both occipital lobes. No abnormality of the brainstem or cerebellum was seen. The arteries forming the Circle of Willis showed moderately severe atheromatous thickening of their walls.

Serial coronal sectioning of the cerebral hemispheres confirmed the severe temporal lobe atrophy. This affected both grey and white matter and in the convolitional white matter of the middle and inferior temporal gyri of each lobe there was a minute vacuolation. In addition, the anterior insula of each hemisphere showed severe wasting. In the frontal lobes the cortex was thinner than normal and there was an obvious diminution in the bulk of the central white matter. The basal ganglia, and in particular the caudate nuclei, appeared to participate in this atrophy. There was a marked compensatory dilation of all compartments of both lateral ventricles, especially of the body of the left lateral ventricle and of both temporal horns, and of the third ventricle.

*Microscopic Observations:* In the cortex of the atrophic temporal lobes there was almost complete loss of nerve cells and all trace of the normal architecture and lamination had been lost. The few remaining nerve cells were found mainly in the inner half of the cortex and these showed chromatolysis or shrinkage and nuclear pyknosis. There were no ballooned nerve cells and sections stained by the von Braunmühl technique failed to demonstrate argyrophilic, intra-cytoplasmic inclusions, neurofibrillary tangles or senile plaques. Throughout the cortex, but mainly at the cortical margins, there was widespread proliferation of astrocytes forming a fibrillary meshwork. The response of the microglia and oligodendroglia was poor. In the white matter there was extensive loss of myelin with status spongiosis, and the fibrillary gliosis was isomorphous in character. There were numerous corpora amylacea. The leptomeninges showed slight fibrous thickening with a histiocytic infiltration of the subarachnoid space.

Similar changes were observed in sections from the frontal lobes but the residual nerve cells and fibres were more numerous than in the temporal lobes, and some trace of cortical lamination remained. No ballooned cells, argyrophilic inclusions, neurofibrillary tangles or senile plaques were seen. Apart from marginal fibrillary gliosis, astrocytosis was not marked and there was only slight thinning of myelin.

In the parietal and occipital lobes there was only minimal loss of ganglion cells and no appreciable demyelination.

There was possibly some slight loss of nerve cells from the caudate nucleus and putamen of each hemisphere but no obvious demyelination or gliosis. There was no recognizable outfall of nerve cells from the thalamus but many of the cells contained a large amount of lipofuscin and showed chromatolysis. An occasional cell was undergoing neuronophagia. No other abnormality was seen.

In the midbrain there was slight loss of nerve cells from the substantia nigra with scattering of melanin pigment in surrounding tissues and slight gliosis. In each cerebral peduncle there was obvious demyelination and gliosis in the frontopontile and temporo-pontile pathways.

No cerebellar abnormality was seen.

In all sections the arteries showed moderately severe atheroma but there was only minimal thickening of the arterioles.

## SURVEY OF CLINICAL FEATURES

*Family History:* There was no history of Pick's disease in the forebears or collaterals. These cases, therefore, fail to corroborate the hypothesis of genetic transmission. (Grünthal, 1930; Sjögren, Sjögren and Lindgren, 1952.)



*Previous Injuries and Illnesses:* Case 2 had what was probably a mild depressive illness in her twenties, and at the time the first changes in personality were noted was struck in the face with a shuttlecock. Case 3 sustained a moderately severe head injury at the age of 21, and suffered from recurrent malaria in her middle twenties.

*Age of Onset* was during the sixth decade.

*Duration of Disease* varied from eight to fourteen years. It was notable that none of the patients required hospital supervision until a late stage of the illness.

*Course of Disease* seemed to fall naturally into three phases, as described by Schneider (1929). In our three cases these could be summarized as follows:

- (a) A first stage, characterized by personality change and impaired judgment.
- (b) A second stage, characterized by the appearance of localizing signs (e.g., aphasia) on a background of progressive mental deterioration.
- (c) A terminal stage of mutism and extreme hebétude.

It seems important to stress that in this syndrome of slowly progressive mental deterioration, in which the evolution of symptoms followed a strikingly similar course from case to case, we found that the details of the history provided even greater diagnostic help than the examination findings for these last naturally depend on the stage at which the patient is first seen. It is even conceivable that the wide variation in symptomatology of reported cases of Pick's disease may be attributable in part to an understandable tendency on the part of authors to emphasize the "cross section" findings at clinical examination rather than the longitudinal survey of these personality and intellectual deficits, which by their cumulative effect on behaviour finally bring the patient under observation. Therefore, in the discussion which follows, we have made no arbitrary division between the facts reported by the relatives and those noted after the patient's admission to hospital. In our tabulation of symptoms, we have allowed ourselves one chronological inconsistency: discussion of the somewhat complex personality changes appears at the end of this section, although these were the first manifestations of the disease process.

## 1. PHYSICAL SIGNS

(a) *Pain:* In all three patients, mild pressure applied to any part of the body appeared to cause pain, while deep pressure and minor painful stimuli, such as pinprick or venepuncture, called forth vocal and facial expressions denoting acute pain. These findings were corroborated by the nursing staff during routine nursing attention. This generalized hyperalgesia was most pronounced in Case 1 whose relatives had noted it some four years before her admission to hospital. In Case 2, a single woman living alone, the onset of this phenomenon could not be assessed, while in Case 3, it was so inextricably linked with her complaint of "rheumatic" pain that her relatives had not at any time distinguished it as a separate entity. Conversely, at no time while they were under our observation, could we convince ourselves that these patients suffered from spontaneously erupting pain. Their attitude at rest did not denote suffering. The previous histories of cases 1 and 3 indicated, however, that such "spontaneous" pain had been a feature of an earlier phase

of the illness. In course of time, the generalized hyperalgesia so strikingly evident at the time of their admission gradually disappeared and could no longer be elicited at the end of a year's hospitalization.

Occasional fleeting reference is made to pain as a symptom in the clinical records of reported cases of Pick's disease. Reich (1905, 1907), in a very detailed account of a male patient with Pick's disease, states that the relatives reported his having excruciating pains some years before admission to hospital. Schneider (1929) states that one of his patients complained of pain in the left arm for which no physical cause could be found. Bouton (1940) mentions pain as a symptom in two of his four cases of Pick's disease. In the first, a complaint of right-sided pain was ascribed to the condition of cholelithiasis found at necropsy. The second patient, a man of 61, was assumed to be suffering from somatic delusions, because in addition to frontal and occipital headache, he complained of a "pricking sensation in his skin, and of pain about the waistline and lower back". Reporting a series of eight cases, Schenk (1951) describes one in which the symptom of pain closely resembles that which we observed. The patient, a woman of 57, had a history of rheumatism of several years duration, and when she came under care in hospital it was recorded that "elle se plaint de douleurs au moindre contact".

The bizarre pain reactions of our three patients call to mind the "thalamic over-reaction" phenomenon of excruciating pain arising spontaneously and/or as an exaggerated response to stimulus. Accepted as generally denoting a vascular lesion in or adjacent to the thalamus, this phenomenon is said to follow, albeit more rarely, other types of lesion in this area. No such vascular lesion was demonstrated post mortem in our three cases. Moreover, when sections of the thalamus were examined with particular care, as in Case 3, no significant abnormality was found. While it is part of traditional neurological belief that excessive response to painful stimuli and severe "spontaneous" pain betoken a thalamic lesion, there are nevertheless cases on record to show that this so-called "thalamic over-reaction" phenomenon can occur with cortical lesions. Marshall (1951), writing on sensory disturbances in cortical wounds with special reference to pain, describes two cases of hyperalgesia following cortical wounding and refers to similar observations made by Kleist (1922) on head wounds of the 1914-1918 war. He also cites reports by Guillain and Bertrand (1932) and Davison and Schick (1935) which showed that spontaneous pain and hyperpathia have been found in association with cortical lesions without involvement of the thalamus. One of us (Robertson, 1953) has witnessed hyperalgesia in association with a subdural haematoma overlying the right frontal lobe.

It is possible that this symptom occurs more frequently in Pick's disease than the published cases would suggest. It is easy to see how it could be overshadowed by the general mental devastation. Alternatively, our observation that the hyperalgesia disappeared within a year of hospitalization argues that this symptom may only be elicitable during a particular phase of the disease.

(b) *Obesity*: All three patients showed a moderate obesity, and, perhaps more strikingly, retained this obesity as the disease progressed.

(c) *Hypersomnia*: Cases 1 and 2 exhibited hypersomnia before admission to hospital, and in the latter stages of their illness, all three slept soundly throughout the night and for long periods during the day. Nocturnal restlessness was never noted.

(d) *Other Physical Signs*: Case 1 developed a "gorilla" gait with bowed trunk and arms hanging limply by her side. Case 2 developed a lopsided posture—with trunk inclined to the right, a shuffling gait, exaggerated proprioceptive reflexes and munching movements of the jaws. Finally, she became bedridden with right-sided paresis and generalized muscular rigidity, but without definite pyramidal signs. Case 3 latterly developed a mask-like facies and mild dysarthria, in that she stuttered over the first syllables of her few remaining utterances. (Case 3 was the only patient to exhibit even a mild degree of dysarthria, and this as a terminal phenomenon.) Anomalies of gait, posture and muscular tonus are frequently reported in Pick's disease (Thorpe, (1932), Caron (1934), Ferraro and Jervis (1936), Becker (1948)), but their late appearance in the course of the disease, their variability, and their frequent occurrence in other types of presenile and senile dementias decreases their value as an aid to the diagnosis of Pick's disease.

## 2. APHASIA

This appeared five or six years after the personality changes, presented initially as a defect in noun-finding ("she forgot the names of things") and steadily progressed to a gross reduction in all elements of speech with a concomitant decreased understanding of the conversation of others. To compensate for their amnesia for words, these patients (a) employed circumlocutions, (b) used generic terms such as "thing", "man", "woman", (c) made one word convey several shades of meaning. (Case 3 used "lucky" not merely to mean "fortunate" but to denote anything considered good, valuable, useful or attractive), (d) selected from their restricted vocabulary substitute words, where the underlying association was not immediately apparent, (Case 2 used "glasses" for "money" presumably because both words denoted objects of extreme personal value). All three patients confused words denoting gender and family relationships. On occasion, they employed surprisingly elaborate adjectives and adverbs. They made accurate use of numbers and also of simple adverbs of place, e.g., "up" and "down". Increasing familiarity with their individual vocabularies and turns of phrase enabled the examiner to acquire considerable information from their spontaneous conversation whereas direct question and answer methods were less productive. This was not wholly attributable to their diminished comprehension. These patients showed a marked disinclination to listen to questions, particularly those questions which did not touch on their immediate personal concerns. In spontaneous conversation they appeared to have a clear mental image of what they wanted to express and made strenuous efforts to mobilize their limited vocabulary to this end. They rarely resorted to pantomime. They showed no dysarthria or paraphasia. Perseveration was marked. Case 1 at every interview introduced an anecdote relating to her recently dead husband. Cases 2 and 3 repeated similar anecdotes and in addition had a collection of standard phrases which they interpolated into every conversation. (A tape recording of the conversation of Case 3 strikingly illustrated her frequent reiteration of three phrases—"I'm not joking"—"I'm really disgusted"—"it's awfully lucky").

Reading and writing abilities were difficult to assess because of marked disinclination to submit to testing. All signed their names on admission, but could seldom be persuaded to do so thereafter. Cases 1 and 3 read printed name cards with occasional mispronouncement. Case 1 studied magazines with such earnestness that she gave the impression of acquiring information from either typescript or illustrations. Case 2 had given up reading newspapers



many years previously and seemed genuinely unable to read name cards. All patients recognized numbers, and Case 2 when taken on an expedition to her home, identified tram cars by their numbers. Case 3, when taken on a similar expedition to her club, recognized the various rooms by their printed signs, e.g., "Lounge", "Dining Room". It seemed therefore that the stimulus of practical necessity could evoke recognition of symbolical visual signs until a late stage of the disease.

When in the course of time these patients passed into their final stage of hebétude, the transition from spontaneous speech to relative mutism was accomplished swiftly with no intervening paraphasia or dysarthria. In this final stage, an external stimulus in the form of human greeting could still elicit remnants of their former conversation, such fragmentary phrases being repeated in a mechanical way as though a memory echo of former statements. (Case 3 murmured disjointedly "I'm really disgusted—I never realized—along in that place, dear, with all the proper bonny things".)

It is perhaps worth noting here that Cases 1 and 3, both of whom had musical training, retained a sense of rhythm and melody until a late stage of the illness.

Published cases of Pick's disease in the English and American literature contain few detailed analyses of the speech disturbance exhibited, and the comment generally made by the authors is that all types of aphasia are to be found (Thorpe (1932), Kahn and Thomson (1934), Ferraro and Jervis (1936), Nichols and Weigner (1938)). More elaborate studies have been carried out by Continental writers, influenced presumably by Pick's original emphasis on aphasia, and these have been analysed by Caron (1934). Caron catalogues such characteristic features as loss of memory for words, compensatory periphrases, preservation of syntax, normal articulation, and absence of paraphasia or jargon. He refers to the extreme reduction in speech in the final stage and to the iterative phenomena: "certain memories are conserved and reiterated monotonously." He quotes Stertz (1926) for the observation that these last always require an external stimulus for their production (as in our three cases) but he himself does not consider that this rule invariably applies. He emphasizes the patients' disinclination to submit to formal testing, and says that this trait has been noted by many observers.

The iterative phenomena call for further comment. That some or other type of perseverated utterance occurs frequently in Pick's disease is generally agreed (Kinnier Wilson, 1940), and is cited, even by those authors who otherwise make little detailed analysis of the aphasia, as a valuable diagnostic sign. It is understandable that the patient's repetition of stereotyped phrases should compel the attention of the observer, particularly when these appear in florid form, as in Case 3, of our series. Nevertheless, such iterative phenomena, whether taking the form of echolalia, pallilalia or verbigeration, occur in many types of cerebral lesion and we do not consider that they should be given predominance over the other aphasic features in conferring the diagnosis of Pick's disease. The aphasic features minutely described by certain Continental authors, e.g., Rosenfeld (1909), Stertz (1926) and Schneider (1927) and cited in Caron's monograph closely resemble those observed in our three cases. Such features conform, in general, to the type of aphasia designated "nominal" or "amnestic". Writers in the past, including Pick himself, have held that amnestic aphasia denotes a temporal lobe lesion; but it has also been reported to result from focal lesions in the parietal lobe (Head, 1920; Nielsen, 1946). To explain the remarkable uniformity of the aphasic

picture in our three cases, it seems permissible to incriminate both the disease process itself and also the cerebral areas on which its effects are exercised. It could then be postulated that a specific disease process with a predilection for the temporo-frontal lobes is responsible for the uniform type of aphasia in the cases of Pick's disease here described.

### 3. SPATIAL MANIPULATION AND TEMPORAL ORIENTATION

Since all three patients suffered from a slowly progressive dementing syndrome, their concepts of space and time were inevitably impaired. Nevertheless, they showed a conspicuous absence of many of those spatial and temporal defects which have been investigated and enumerated in lesions of the parietal lobe (Critchley, 1953). In order to demonstrate this, we have followed as far as it was possible to do so, Critchley's list of these diverse "interdimensional spatial manipulations" the successful performance of which seems to depend on intact functioning of the parietal lobe.

A topographical sense was relatively intact until a late stage of the disease. Before their admission to hospital, all three patients journeyed unaccompanied through a large and busy city, and these journeys might involve boarding a series of buses and trams. They quickly orientated themselves in a hospital block of many wards and corridors and retained this ability as long as they were ambulant. Their capacity to perform certain relatively complex tasks, e.g., cooking and mending, showed that they were able to construct and manipulate objects, admittedly with impaired finesse. All three were still playing card games at home. (Case 1—Patience, Case 2—Rummy, Case 3—Bridge), although it was known that their proficiency had declined. In hospital it was noted that Case 2 could follow embroidery patterns while Case 3 completed 200-piece jig-saw puzzles with speed and dexterity. They were usually able to point to parts of the body on command, and showed no defect of laterality. No "dressing apraxia" was demonstrated during their first year in hospital; none required help in feeding or washing, and Case 3 could apply cosmetics effectively. All three patients could tell the time on a clock face. Cases 2 and 3 used the adverbs of place, "up" and "down" correctly.

If under the heading of spatial manipulation we include, as does Critchley (1953) "the conception of time or order or sequence", then it can be added here that all three patients must have had a clear conception of the links in a chronological sequence, otherwise they would not have been able to carry out their rigid programme of activities. In other words, they were able to build up chains of associations, the separate items of which were linked by their purely temporal connections. Their preservation of other aspects of temporal awareness may be tabulated as follows: (a) Cases 1 and 3 could assess the time of day without reference to a clock, (b) Cases 2 and 3 could gauge the passage of time in that they assessed their length of stay in hospital in the appropriate number of weeks. This illustrates how some aspects of temporal orientation are dependent on at least a primitive numerical sense. (It was notable that all three patients frequently interpolated numbers into their conversation—possibly to compensate for their verbal impoverishment—and Cases 1 and 3 could give the ages of their three children even when unable to remember their Christian names.)

The functions which we have included under the somewhat clumsy title of "spatial manipulation and temporal orientation" are frequently ignored in published cases of Pick's disease. Certain authors refer briefly (without

adducing examples) to the patients' defects in these spheres. Caron (1934), for instance, states that orientation is impaired early in the disease. Kinnier Wilson (1940) gives a similar opinion: "onset is as a rule insidious, among the first symptoms being a poor memory and a tendency to confusion in respect of space and time." Conversely, Ferraro and Jervis (1936) state that orientation was fairly well preserved in their case. Mayer-Gross, Slater and Roth (1954) in their textbook say that "the dementia progresses rapidly with increasing disorientation and loss of contact with the surroundings", but later, in discussing the differential diagnosis of Pick's disease and Alzheimer's disease, they add, "on the whole the picture in Alzheimer tends to be dominated by parietal lobe symptoms and in Pick by frontal lobe symptoms". Admittedly, it is only during the last two decades that attention has been focused on these spatial and temporal defects which are found in association with parietal lobe lesions (Russell Brain (1941), Critchley (1953)), so that now there is a general awareness of what constitutes the so-called parietal lobe syndrome. It may be that this relatively recent elucidation of parietal lobe symptomatology explains why so little reference was made to these aspects of Pick's disease by earlier writers. Certainly in our three cases the absence of such "parietal lobe signs" was one of the most striking features to emerge at examination and seemed to us to carry the strongest diagnostic presumption that the cerebral lesion, in its initial stages at least, involved the anterior part of the brain.

#### 4. MEMORY

The rigid timetable of activities carried out by all three patients in the period preceding hospitalization indicated at one and the same time an impairment of memory functions and the ability to compensate for such impairment. Their spontaneous conversation in hospital revealed that they remembered personal experiences in the immediate and recent past. They rarely alluded to their childhood or the remote past, thus presenting a striking contrast with patients suffering from senile dementia. Specific questions designed to test recall of this or that event met with an inconstant response, but here again the response was more likely to be accurate when the question concerned events of recent or contemporary interest. They displayed no interest and made no response when questioned about those outstanding world events which form the basis of routine memory tests.

Various writers have emphasized the relatively good retention of memory functions in the first two stages of Pick's disease (Kahn and Thompson (1934) Nichols and Weigner (1938) and Malamud and Boyd (1940)). Memory comprehends many components, the analysis and synthesis of which have been but imperfectly explored. It may be that the ability to orient oneself in space and time represents a special aspect of memory, and in this our patients were not notably deficient. It has to be borne in mind that our patients suffered from a severe degree of amnesic aphasia which must affect memory in its higher conceptual aspects, and in addition renders difficult the testing of memory functions since the patient is not always able to understand the import of questions. This latter fact does not always seem to be taken into consideration by the authors of many of the reported cases of Pick's disease, who cite the responses to verbal questions as evidence of gross memory defects. In assessing the degree of memory impairment in aphasic patients, a careful study of their behaviour before and during hospitalization is essential. The evidence supplied by the behaviour and restricted speech of our patients indicated that



they recollected many of the simple and concrete facts of their daily existence, that they were able to fit these into a chronological sequence and were able to anticipate the immediate future.

## 5. PERSONALITY CHANGES

(a) "*Selfishness*": One of the earliest changes noted in the histories was a restriction of the field of interest to immediate personal concerns, variously interpreted by the relatives as "selfishness", "egocentricity", or even "apathy" and "laziness". Inquiry showed that "apathy" and "laziness" referred to diminished performance of communal tasks or duties towards others. By contrast, the patients continued to pursue their own individual aims with accustomed and even accentuated vigour. They displayed a notable self-sufficiency, and were able to provide for their material wants and indulge in favourite pastimes until a late stage of the disease. This was most strikingly illustrated in Case 2, a single woman, who carried on an active, if somewhat erratic, existence, without external care or supervision until her admission to hospital.

(b) "*Rigidity*" (*stereotypy*) and "*obstinacy*" (*perseveration*). At a somewhat later stage, certain qualities described by the onlookers as "rigidity" and "obstinacy" made their appearance.

(i) "*Rigidity*" (*Stereotypy*): All three patients gradually evolved an unvarying programme of activities. They adhered to a strict routine in their performance of domestic tasks, and allocated their various social and shopping expeditions to certain fixed days of the week. Case 3 went out every day, and her husband could always foretell the object of each daily excursion. Case 1 collected her pension and carried out certain errands on the same days of each week. Case 2 lived alone and was not subject to the same observation as the others, but her rigid adherence to a timetable was illustrated in her domestic tasks and by her turning up at church one hour late after the introduction of Summer Time. This rigidity was illustrated also in minor actions (sometimes with laudable results, since Case 3 invariably bought herself two whiskies when visiting her club, and was never known to exceed this number).

(ii) "*Obstinacy*" (*perseveration*): Closely related and yet dissimilar, was a quality usually described as "obstinacy". Once these patients started an action, they could not be deflected from their individual mode of terminating it. Case 1 continued to scatter crumbs for the birds in the garden although she knew that she was expected to use a recently erected bird-tray. Case 3 acquired the habit of placing plates of soup in the oven to heat, and could not be dissuaded from this although it was pointed out that the resultant pellicle rendered the soup unpalatable. The complex patterns of some of these perseverating actions concealed their essentially compulsive nature. Observers therefore often assumed that the patients' exasperating persistence indicated wilful malice.

(c) "*Restlessness*": This trend was never reported by relatives, but was a notable feature of the patients' conduct for a time after admission to hospital. Cases 1 and 2 rummaged endlessly in the drawers and lockers, withdrawing and examining articles of clothing. Case 3 perambulated the corridors, peering into all rooms encountered on her route, and spent long

periods beating time to a whistled tune by tapping her feet and slapping her thighs.

(d) "*Social Judgment*": There was a general blunting of social judgment, tact, self-criticism and self-restraint. All the patients discussed personal and intimate matters with strangers. Case 3 had indulged in persistent shoplifting for some years prior to admission; and Case 1, during the funeral service for her husband, was pre-occupied with a search for some of his personal belongings. None of the patients appeared to be influenced by the opinions and reactions of others, whether censure or praise, and pursued their simple aims unhindered by any but physical obstacles.

(e) "*Mood*": None of the patients was ever observed to weep and none ever displayed any sign of sadness or distress. The predominant emotional colouring in Case 1 was stolid placidity, in Cases 2 and 3 bland, facile euphoria, interrupted on occasion by fleeting irritability and aggression. Bereavements were dismissed with perfunctory expressions of grief. Case 1 said of her husband: "I was awful vexed when I lost him", and Case 3 said of her son's death: "It was really very bad luck." These expressions could not be entirely attributed to reduced vocabulary, for the patients were able at this time to give forceful, if periphrastic, expression of opinion on matters which aroused their interest, and the matter-of-fact form of their statements on their bereavements was matched by their matter-of-fact manner in making them.

(f) *Reaction to Testing*: A striking feature was the *disinclination to co-operate in formal testing*. In this the patients differed markedly from others with a like degree of organic deterioration. Only rarely would they attempt the tests presented to them, and if the examiner insisted they became querulous. They never showed the "catastrophic reaction" of emotional distress in response to failure at a task. They rarely confabulated. Sometimes they used inappropriate facile excuses to explain their inability to perform a task, e.g., "I need my glasses, you see I live alone" (Case 2).

*Comment on Personality Changes*: It is generally agreed that emotional and personality changes dominate the clinical picture in the early stages of Pick's disease. It seems unlikely, however, that these changes in the sphere of so-called "personality" are entirely independent of intellectual deterioration. Primary emotional changes, caused directly by cerebral damage, are no doubt present; but we believe that the results of these changes become elaborated and extended because of a compelling need of the organism to compensate for failing intellectual powers. In the early stages of such an illness the intellectual deficits can still be covered up in various ways, and it is the resulting compensatory, "personality" changes that are reported by witnesses. For example, the "selfishness" of our patients seemed to imply not only a *lack of emotional interest in other people*, but also a *narrowing of their defective powers of attention to those stimuli subserving their own most essential needs*. Such canalization of interest enabled them to lead a relatively independent existence despite their failing capacities. Their *stereotypy and perseveration* can be understood in a similar way. It is not difficult to accept that *a simple rigid outlook may result from primary emotional blunting*. In addition, however, these patients were being left with progressively less

mental equipment for dealing with their environment. They were therefore compelled to *sacrifice their flexibility and adaptability in order to simplify their needs and activities*, thus keeping the pattern of their lives within the scope of their reduced abilities. These features recall some of the "adjustments" of behaviour in brain lesions described by Goldstein (1936, 1940), who believes that they occur automatically, when the total situation of the organism demands them, without training, conscious striving, or even awareness, on the part of the individual.

Some of the personality changes which we have enumerated have been mentioned already in published cases of Pick's disease, although the descriptive term utilized may not be the same. The terms "emotional apathy" and "indifference", used by certain writers, seem to refer to the quality which we designated "selfishness". The stereotypy of behaviour which was such a prominent feature in all our cases does not appear to have been emphasized as a pathognomonic trait, except by Nichols and Weigner (1938), who mention that their patient "became stereotyped in the discharge of her household duties, preparing the same meal day after day". The peculiar reaction of these patients to formal testing has been noted by several writers. Caron (1934) and Ferraro and Jervis (1936) have commented on the difficulty in holding the attention of patients with Pick's disease. Stertz (1926) speaks of "their profound aversion to respond by speech . . . their absolute refusal to name, to repeat and to write". Stertz considered that this was dependent on a primary inertia, but Pick (quoted by Caron) believed that it arose from the patients' realization of their own defects. We believe that this reaction is but another facet of the trait we have previously designated "selfishness". As such it may be held to depend on both (a) a primary emotional change and (b) an attempt of the organism to compensate for failing intellectual powers by ignoring all extraneous stimuli which do not subserve material needs.

#### PATHOLOGICAL FINDINGS

The pathological changes in all three cases were basically the same. All showed a severe symmetrical atrophy of the temporal lobes (although minor differences existed on the degree of involvement of the individual temporal gyri). All showed a less severe and less uniform atrophy of the frontal lobes. The parietal and occipital lobes seemed scarcely affected by the disease process. Microscopically the salient feature was an outfall of ganglion cells from atrophic gyri. No neurofibrillary tangles, no argyrophilic inclusions and no ballooning of nerve cells were found. Argyrophilic plaques were also absent.

#### CONCLUSIONS

These cases presented a picture in which there was undoubtedly a generalized mental deterioration, but in which certain faculties stood out for their relatively good retention, alongside a very pronounced loss of others.

By far the greatest impairment was seen in the speech functions (all three patients exhibited a uniform type of amnesic aphasia), and in what may be termed the sphere of personality, i.e., mental functions that are known to become impaired in lesions of the temporal and frontal lobes. These patients lived in the present; they concentrated their energies and attention on their own persons, interests and needs; and they very early showed a marked falling off in altruistic identification, social responsiveness and inhibition.



The relatively good retention of memory in Pick's disease has been frequently commented on, but the comparative preservation of abilities which have come to be associated with the parietal lobes (awareness, understanding and manipulation of spatial and temporal relationships) has, we consider, been insufficiently emphasized in the past.

The physical signs common to all the cases were generalized hyperalgesia, somnolence, obesity and—in the final stages—anomalies of posture and muscular tonus. Of these, hyperalgesia, because of its rarity in neurological syndromes generally, was regarded as an important diagnostic sign.

A fairly constant pathological background was found to underlie this remarkably uniform clinical picture.

In order to arrive at a diagnosis, a detailed history of the development of the illness was found to be as important as repeated mental examinations. It is suggested that, with this proviso, it is not difficult to differentiate this variant of Pick's Disease from other dementias of the presenile period.

#### SUMMARY

Three cases of Pick's disease, confirmed at autopsy, are reported.

A hypothesis regarding the differentiation of this condition from other pre-senile dementias on clinical grounds alone was made during the study of the first case; and this hypothesis was tested and verified when the other two cases were encountered.

The clinical features are discussed, and special reference is made to a generalized hyperalgesia displayed by all three patients.

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# A RETROSPECTIVE CONTROLLED STUDY OF LEUCOTOMY IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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THE controlled study of the major physical treatments in schizophrenia (and other psychiatric conditions) has been retarded by the view that it is unethical to withhold treatment from the patient. Although this argument is clearly dubious until a treatment is proved, the number of forward-looking controlled studies of E.C.T., insulin coma therapy and leucotomy may nevertheless be counted on the fingers of two hands. Not all schizophrenics have, however, received every possible treatment, and if it were possible to make comparisons of treated and untreated cases retrospectively, there would be no ethical objection to overcome.

The essentials of any controlled study of treatment in schizophrenia are:

1. That the treated and untreated groups should have had the same regime apart from the treatment being examined.
2. That the treated and untreated groups should have been under care at the same time.
3. That the groups should consist of similar cases and have the same prognosis or the same tendency to "spontaneous remission".

In an earlier paper (Robin, 1958) assessing leucotomy it was shown that sex, age on admission and length of admission were prognostic factors. The method used in that study was as follows:

Each leucotomy patient was matched with a patient of the same sex, of the same age on admission (in 5-year blocks), admitted nearest to the date of admission of the leucotomized patient (in 3-month blocks) and still in hospital at the time when the leucotomized patient had the operation.

This method, it will be seen, ensured that the patients were treated at the same time. If the patients are followed up for a long enough period it can be assumed that any special treatment programme will not survive, and in this respect it has already been shown elsewhere that "total push" programmes have only a temporary and concurrent effect (Bennet and Robertson, 1955).

Penrose (1947) describes a similar method which likewise did not use diagnosis as a factor in matching. Nevertheless, Penrose (1947) shows that all three factors used are related to diagnosis. First, length of admission determines the number of schizophrenics in a group—the longer the stay in hospital the greater the chance that the diagnosis will be of schizophrenia. Secondly, age on admission may be divided into four periods—corresponding to four diagnostic groups—"epileptic-defective", "schizophrenic", "affective", and "senile-organic". Finally, sex differences are also noted in different diagnoses—schizophrenia is commoner, occurs younger and is therefore more serious in males; affective disorders in females. Groups chosen for sex, age or length of admission

do, in fact, as has been shown in the earlier paper (Robin, 1958), match well for diagnosis. If, however, diagnosis is added as a factor in matching, and pairs are now chosen not only for sex, age on admission, length of admission but also for the diagnosis of schizophrenia, matching is extremely close for many other factors. Of the 198 pairs considered in the earlier study, sixty were found to match for the four factors to be used. These cases were studied in greater detail and are presented here.

(a) 60 PAIRS MATCHED FOR SEX, AGE ON ADMISSION, LENGTH OF ADMISSION AND SCHIZOPHRENIA

A. *A Comparison of the Treatment and Control Groups*

Of the leucotomized patients, 52 had a single operation and 8 had more than one operation. The 60 pairs corresponded exactly in their sex distribution (C.1.), closely as far as age on admission (C.2) and the period of admission prior to operation (C.3) were concerned. This matching, of course, had been designed. By examination of the case records the leucotomized and control groups thus selected were, however, shown to be comparable also as far as:

1. Total length of previous admissions to Runwell Hospital (C.4).
2. Total length of previous admissions to other mental hospitals (C.5).
3. Civil state (single, married, etc.) (C.6)
4. Occupational record as far as stability is concerned (C.6)
5. Family history of mental illness and suicide (C.6)
6. Type of school attended and progress (C.7)
7. Heterosexual attainment—a history of heterosexual friendships, an engagement, etc. (C.7)
8. Intemperate habits (C.7)
9. Personality type (C.7)
10. Age at onset of first symptoms (C.8)
11. Type of onset of symptoms—acute or insidious (C.8)
12. Response to electroplexy (C.8)
13. The number of remissions in the illness (C.9)
14. The occlusive index (C.9)
15. The immobility index (C.9)
16. The mean weight (in pounds) on admission and at the operation date (C.9) were concerned.

The "occlusive index" was designed by the Columbia Greystone second group (Mettler *et al.*, 1952) as a prognostic test, as was explained in a later paper (Mettler *et al.*, 1954), because "cases with pre-operative histories of interrupted institutionalization had better chances of post-operative release than did cases having equally long (and even shorter) histories of institutionalization without any extramural intervals". This positive prognostic sign was called "mobility" (Crandell *et al.*, 1954) and the index was designed to measure it. The index is obtained (Mettler, 1952, p. 317) by "dividing the sum of the months all patients in a group have been institutionalized by the sum of the number of all interruptions occurring in the records of institutionalization". An "interruption" was defined as "an absence from the hospital lasting 14



days or longer" (Crandell, 1954). The index may, of course, also be used to assess the prognostic potentiality of a control group and, indeed, Mettler (1952) used it in this way.

The "immobility index" (Crandell *et al.*, 1954) is a finer measure using the same principles but allegedly suitable for individual cases. It has been validated in a large series of patients admitted in 1939 to New Jersey State Hospital and followed to determine outcome for 13 years. "The immobility index for individuals is obtained by dividing the total number of days of hospitalization within the first two years after the first admission by the number of moves into hospital, counting the first admission as move 1". A fourteen day break again counts as a discharge. Crandell *et al.* (1956) later conceded that the index might be calculated in months and not days.

Finally a comparison of physical treatments used on the leucotomy and control groups before operation date was undertaken (C.8) and this showed similarity in the frequencies of employment of five of the six treatments considered. As far as prolonged narcosis was concerned a significantly larger number of leucotomies had thus been treated than controls. Whether this is meaningful or not it is difficult to say. Two facts should be first considered. By chance in a large number of comparisons some (1 in 20 if the 5 per cent. level of confidence is used) may be expected to appear significant.

Secondly the "operation date" for the controls was merely an arbitrary point in time. If the *total* treatment in both groups before and after operation date is examined there are no significant differences in the number treated or the type of treatment given.

### B. Behaviour Ratings

In order that an accurate comparison might be made of behaviour in the two groups the method of time sampling was used. Each patient's behaviour was studied from the case records for three months after admission. This period was selected as the patients had then been submitted to the same procedure and therefore this period of time was equally meaningful to both groups. Secondly, psychiatric notes tend to be much more detailed in the early days after admission and to become progressively more routine thereafter.

The behaviour rating was based on the Malamud-Sands Scale (1947) but the items were adapted in the light of Runwell Hospital case records which are written according to a fairly uniform pattern and thus provide fairly uniform information.

It will be seen that this time sampled behaviour record (C.10, etc.) shows the leucotomy and control groups to be comparable in:

1. General appearance (C.10).
2. Motor activity (C.10).
3. Aggressiveness (C.10).
4. Suicidal inclination (C.10).
5. Sleep rhythm (C.10).
6. Socialization (C.11).
7. Attention (C.11).
8. Speech (C.11).
9. Nutrition (C.11).
10. Hospital work undertaken (C.12).

11. Mood (C.12).
12. Affect (C.12).
13. Awareness (C.12).
14. Presence of thought disorder (C.13).
15. All categories of thought content studied except delusions (C.13).

Delusions were expressed more frequently by the leucotomized group. Once again it must be borne in mind that this could be a chance difference.

In summary, it is clear that the two groups matched for four leading factors are closely comparable in about thirty other ways which are said to have prognostic implications.

### C. Results

The general results (C.14) show leucotomy to offer no advantage in the treatment of schizophrenia. A larger number of discharges in the leucotomy group is counter-balanced by a larger number of re-admissions. The total period spent in Runwell (C.15) after operation and in all mental hospitals (C.16) is comparable in the treated and untreated groups. Finally (C.17) just as many leucotomized patients required physical treatments after operation as did the controls. The position of the patient from three months to ten years after operation date as far as discharge and death are concerned is shown in the histogram (Fig. 1).

NUMBERS DISCHARGED (TRACED & UNTRACED) UNDISCHARGED & DEAD IN LEUCOTOMY & CONTROL GROUPS MATCHED FOR SCHIZOPHRENIA, AGE, SEX & CHRONICITY 3/12-10 YEARS AFTER OPERATION

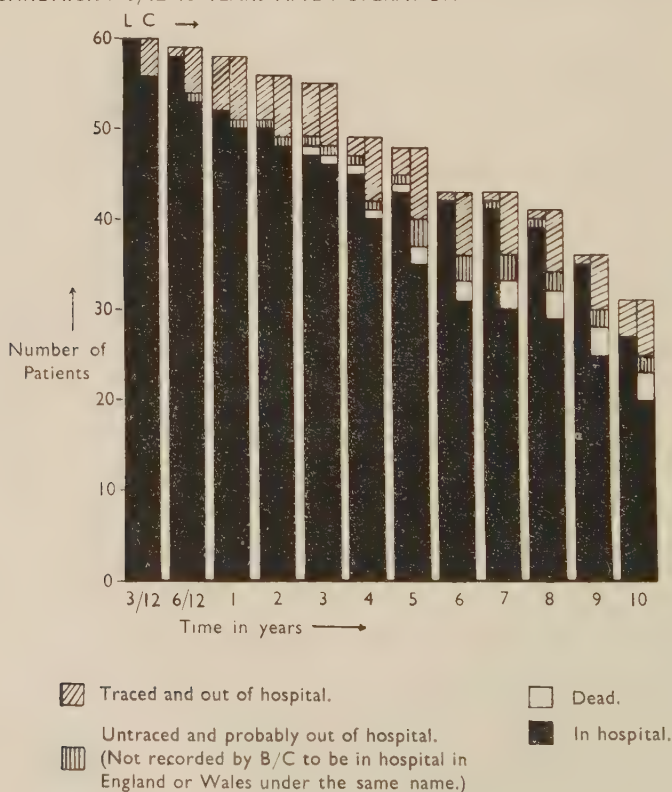


FIG. 1

#### D. *Post-operative Health*

Items considered here (C.18) have been recorded in the case sheets. It is fairly safe to assume that major illnesses are all noted. A good deal of minor ill-health is, even if discovered, often not recorded. It is clear that the epilepsy in the leucotomy series results from the operation. No other items of ill-health (and even certain obvious combinations of these) produce significant differences between the two groups. The incidence of post-operative epilepsy in this group would be 18 per cent.—a high figure reflecting the long follow up.

#### E. *Weight*

As is common in mental hospitals, patients in Runwell Hospital have their weight recorded on admission and thereafter monthly. It has already been stated that the leucotomy and control groups had comparable mean weights on admission and at the operation date. The patient's weight was now extracted from the record from six months to ten years after operation depending on how long the patient remained resident, and expressed as a percentage of the weight at the date of operation. An arbitrary percentage (105 per cent.) was chosen (1) on the basis of inspection of the tables, and (2) because gains greater than this represented roughly a gain of more than 6 pounds on the basis of the mean weights recorded. The results are presented in detail (C.19) and for easy inspection (C.20). It is clear that for roughly two years in diminishing degree larger numbers of the leucotomy patients show significant gains in weight. Thereafter there is no difference in the evidence collected in the two groups. This might have been because the fat leucotomies are discharged and corpulence is a peculiarly favourable prognostic sign of leucotomy. In fact, the evidence (C.21) is against this and patients who showed a significant gain in weight six months post-operatively were equally divided between the never-discharged and discharged groups. By the falling away of the effect after the lapse of time from operation it looks as if the gain in weight is related to the operation.

Experience with insulin (Lipschutz, 1939) is apposite here and while the gain may be some physical (?hypothalamic) effect it may equally be due to special nursing in the period after operation.

#### F. *Hospital Behaviour*

Hospital behaviour has been studied by using the rating scale already described. Initial ratings were made from the case records as before. Ratings of current behaviour were made by the charge nurses of the patient's ward in June, 1957. To obviate bias here, the rating scales were issued through the psychology department where some totally different research on schizophrenia, quite unconnected with leucotomy, had been in progress for over a year. The charge nurses were led to believe that the rating scale was part of this project. Forty-three leucotomy patients and 38 controls were still in hospital on the date mentioned. The ratings show that leucotomy does not appear to alter:

1. General appearance (C.22).
2. Motor activity (C.22).
3. Aggressiveness (C.22).
4. Suicidal inclinations (C.22).
5. Socialization (C.22).
6. Attention (C.23).



7. Speech (C.23).
8. Nutrition (C.23).
9. Sleep (C.23).
10. Mood (C.23).
11. Affect (C.24).
12. Awareness (C.24).
13. Thought disorder (C.24).
14. Thought content (C.24).

More leucotomized patients, however, were employed in occupational therapy and fewer controls were so employed. (For  $n=1$ ;  $\chi^2=4.6$ ;  $p=<.05$ .) This may be a chance finding, an isolated improvement resultant on leucotomy or perhaps the continuation of a habit established in the period of rehabilitation. At any rate, the control patients who no longer attend occupational therapy appear to have been directed into ward work and into the utility departments, both of which, being remunerative employment, are rated as better adjustments than occupational therapy in the hospital.

(b) 19 PAIRS MATCHED FOR SEX, AGE ON ADMISSION, LENGTH OF ADMISSION AND AFFECTIVE DISORDERS

There is no significant difference in the results (C.28) of two groups matched as above (C.25 et seq.).

(c) 12 PAIRS MATCHED FOR SEX, AGE ON ADMISSION, LENGTH OF ADMISSION AND DEPRESSIVE REACTION

There is no significant difference in the results (C.32) of two groups matched as above (C.29 et seq.).

C.1

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

(a) Sex Distribution

|             | Single<br>Leuco-<br>tomies | Controls | Multiple<br>Leuco-<br>tomies | Controls | Total<br>Leuco-<br>tomies | Total<br>Controls |
|-------------|----------------------------|----------|------------------------------|----------|---------------------------|-------------------|
| Men .. ..   | 15                         | 15       | 1                            | 1        | 16                        | 16                |
| Women .. .. | 37                         | 37       | 7                            | 7        | 44                        | 44                |
| Total .. .. | 52                         | 52       | 8                            | 8        | 60                        | 60                |

C.2

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

(b) Age Distribution

| Age on<br>Admission | Single<br>Leuco-<br>tomies | Controls | Multiple<br>Leuco-<br>tomies | Controls | Total<br>Leuco-<br>tomies | Total<br>Controls |
|---------------------|----------------------------|----------|------------------------------|----------|---------------------------|-------------------|
| 16-20 .. ..         | 5                          | 2        | 2                            | 2        | 7                         | 4                 |
| 21-30 .. ..         | 24                         | 24       | 6                            | 6        | 30                        | 30                |
| 31-40 .. ..         | 20                         | 23       | 0                            | 0        | 20                        | 23                |
| 41-50 .. ..         | 2                          | 2        | 0                            | 0        | 2                         | 2                 |
| 51-60 .. ..         | 1                          | 1        | 0                            | 0        | 1                         | 1                 |
| 61-70 .. ..         | 0                          | 0        | 0                            | 0        | 0                         | 0                 |
| Total .. ..         | 52                         | 52       | 8                            | 8        | 60                        | 60                |

## C.3

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## (c) Chronicity

| Period from<br>Admission to<br>Operation Date | Single<br>Leuco-<br>tomies | Controls | Multiple<br>Leuco-<br>tomies | Controls | Total<br>Leuco-<br>tomies | Total<br>Controls |
|-----------------------------------------------|----------------------------|----------|------------------------------|----------|---------------------------|-------------------|
| <1/12 ..                                      | 2                          | 1        | 0                            | 0        |                           |                   |
| 3/12 ..                                       | 0                          | 0        | 0                            | 0        |                           |                   |
| 6/12 ..                                       | 2                          | 3        | 0                            | 0        | 15                        | 16                |
| 1 year ..                                     | 1                          | 5        | 2                            | 1        |                           |                   |
| 2 years ..                                    | 7                          | 4        | 1                            | 2        |                           |                   |
| 3 years ..                                    | 5                          | 4        | 1                            | 1        |                           |                   |
| 4 years ..                                    | 5                          | 5        | 0                            | 0        |                           |                   |
| 5 years ..                                    | 5                          | 2        | 0                            | 0        | 45                        | 44                |
| 10 years ..                                   | 22                         | 25       | 2                            | 2        |                           |                   |
| +10 years ..                                  | 3                          | 3        | 2                            | 2        |                           |                   |
| Total ..                                      | 52                         | 52       | 8                            | 8        | 60                        | 60                |

## C.4

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## (c) Chronicity

## Previous Admissions to Runwell Hospital

| Total Period            | Leucotomies | Total | Controls | Total |
|-------------------------|-------------|-------|----------|-------|
| <1/12 .. ..             | 0           |       | 2        |       |
| 3/12 .. ..              | 0           |       | 2        |       |
| 6/12 .. ..              | 4           | 14    | 3        | 18    |
| 1 year .. ..            | 4           |       | 7        |       |
| 2 years .. ..           | 6           |       | 4        |       |
| 3 years .. ..           | 0           |       | 1        |       |
| 4 years .. ..           | 0           |       | 0        |       |
| 5 years .. ..           | 0           | 0     | 0        | 1     |
| 10 years .. ..          | 0           |       | 0        |       |
| +10 years .. ..         | 0           |       | 0        |       |
| Not previously admitted |             | 46    |          | 41    |
| Total .. ..             |             | 60    |          | 60    |

## C.5

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## (c) Chronicity

## Prior Admissions to Other Hospitals

| Total Period<br>of Admission | Leucotomies | Total | Controls | Total |
|------------------------------|-------------|-------|----------|-------|
| <1/12 .. ..                  | 1           |       | 3        |       |
| 3/12 .. ..                   | 1           |       | 3        |       |
| 6/12 .. ..                   | 0           |       | 3        |       |
| 1 year .. ..                 | 5           |       | 7        |       |
| 2 years .. ..                | 4           |       | 4        |       |
|                              | —           | 11    | —        | 20    |
| 3 years .. ..                | 4           |       | 1        |       |
| 4 years .. ..                | 3           |       | 2        |       |
| 5 years .. ..                | 1           |       | 0        |       |
| 10 years .. ..               | 7           |       | 11       |       |
| +10 years .. ..              | 4           |       | 4        |       |
|                              | —           | 19    | —        | 18    |
| Not previously admitted      |             | 30    |          | 22    |
| Total .. ..                  |             | 60    |          | 60    |

## C.6

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Material Excerpted from Case Records

|                                                            | Leucotomies | Controls |
|------------------------------------------------------------|-------------|----------|
| Civil State:                                               |             |          |
| Single .. .. .                                             | 46          | 49       |
| Married .. .. .                                            | 14          | 9        |
| Separated .. .. .                                          | 0           | 2        |
| Occupational Record:                                       |             |          |
| Stable .. .. .                                             | 22          | 19       |
| Unstable .. .. .                                           | 16          | 14       |
| No information .. .. .                                     | 22          | 27       |
| Family History:                                            |             |          |
| Parents ill and in mental hospital .. .. .                 | 5           | 5        |
| Parents ill and no mental hospital .. .. .                 | 7           | 6        |
| Suicide .. .. .                                            | 1           | 1        |
| "Others" ill and in mental hospitals .. .. .               | 6           | 8        |
| "Others" ill and no mental hospitals .. .. .               | 5           | 8        |
| Suicide .. .. .                                            | 1           | 1        |
| No family history .. .. .                                  | 25          | 22       |
| No information .. .. .                                     | 6           | 9        |
| 1st degree relatives in mental hospital or suicide .. .. . | 10          | 6        |
| 2nd degree relatives in mental hospital or suicide .. .. . | 4           | 7        |

## C.7

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Material Excerpted from Case Records

|                                                         | Leucotomies | Controls |
|---------------------------------------------------------|-------------|----------|
| School attended:                                        |             |          |
| Elementary .. .. .                                      | 35          | 36       |
| Central .. .. .                                         | 2           | 4        |
| Grammar .. .. .                                         | 7           | 5        |
| Private tutor, "Special", Orphanage, etc. .. .. .       | 7           | 7        |
| No information .. .. .                                  | 9           | 8        |
| "Backward" .. .. .                                      | 7           | 9        |
| Heterosexual attainment:                                |             |          |
| Friendship .. .. .                                      | 10          | 10       |
| Engagement .. .. .                                      | 3           | 2        |
| Marriage .. .. .                                        | 14          | 11       |
| No friendships .. .. .                                  | 19          | 18       |
| No information .. .. .                                  | 14          | 19       |
| Habits:                                                 |             |          |
| Intemperance mentioned, sexual licence, alcohol .. .. . | 7           | 4        |
| Personality:                                            |             |          |
| Extraverted .. .. .                                     | 18          | 12       |
| Introverted .. .. .                                     | 30          | 30       |
| No information .. .. .                                  | 12          | 18       |

## C.8

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Material Excerpted from Case Records

|                                | Leucotomies | Controls |
|--------------------------------|-------------|----------|
| Age at onset of first symptom: |             |          |
| Less than 20 years .. .. .     | 17          | 11       |
| 21-30 years .. .. .            | 32          | 38       |
| 31-40 years .. .. .            | 11          | 8        |
| No information .. .. .         | 0           | 3        |



## C.8 (continued)

|                                          |  |    |    |    |    |    | Leucotomies | Controls |
|------------------------------------------|--|----|----|----|----|----|-------------|----------|
| Type of onset:                           |  |    |    |    |    |    |             |          |
| Acute (symptoms less than 3/12 duration) |  | .. | .. |    |    |    | 15          | 9        |
| Insidious                                |  | .. | .. | .. | .. | .. | 31          | 33       |
| No information                           |  | .. | .. | .. | .. | .. | 14          | 18       |
| Physical treatments before operation:    |  |    |    |    |    |    |             |          |
| Electroplexy                             |  | .. | .. | .. | .. | .. | 38          | 35       |
| Leptazol                                 |  | .. | .. | .. | .. | .. | 23          | 20       |
| Insulin shock                            |  | .. | .. | .. | .. | .. | 29          | 23       |
| Modified insulin                         |  | .. | .. | .. | .. | .. | 3           | 5        |
| Prolonged narcosis                       |  | .. | .. | .. | .. | .. | 17          | 6        |
| Drugs, etc.                              |  | .. | .. | .. | .. | .. | 4           | 7        |
| E.C.T. Response:                         |  |    |    |    |    |    |             |          |
| Good                                     |  | .. | .. | .. | .. | .. | 6           | 5        |
| Fair                                     |  | .. | .. | .. | .. | .. | 8           | 14       |
| Poor                                     |  | .. | .. | .. | .. | .. | 25          | 22       |
| Not used                                 |  | .. | .. | .. | .. | .. | 22          | 19       |

## C.9

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Material Excerpted from Case Records

|                              |    |    |    |    |    |    | Leucotomies | Controls    |
|------------------------------|----|----|----|----|----|----|-------------|-------------|
| Remissions in history:       |    |    |    |    |    |    |             |             |
| 0                            | .. | .. | .. | .. | .. | .. | 35          | 34          |
| 1                            | .. | .. | .. | .. | .. | .. | 13          | 14          |
| 2                            | .. | .. | .. | .. | .. | .. | 5           | 6           |
| 3                            | .. | .. | .. | .. | .. | .. | 2           | 1           |
| >3                           | .. | .. | .. | .. | .. | .. | 3           | 2           |
| No information               |    |    | .. | .. | .. | .. | 2           | 3           |
| Occlusive index              |    |    |    |    |    |    | 135.5       | 131.1       |
| Immobility index (in months) |    |    |    |    |    |    | 17.87± 9.05 | 17.87± 7.47 |
| Mean weight in lbs.:         |    |    |    |    |    |    |             |             |
| On admission                 |    |    | .. | .. | .. | .. | 117.4 ±20.6 | 122.0 ±26.6 |
| At date of operation         |    |    | .. | .. | .. | .. | 116.9 ±20.0 | 119.5 ±18.6 |

## C.10

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Time Sampled Behaviour Record

(Behaviour exhibited in first 3 months after admission)

|                 |    |    |    |    |    |    |    | Leucotomies | Controls |
|-----------------|----|----|----|----|----|----|----|-------------|----------|
| Appearance:     |    |    |    |    |    |    |    |             |          |
| Neat            | .. | .. | .. | .. | .. | .. | .. | 30          | 35       |
| Untidy          | .. | .. | .. | .. | .. | .. | .. | 30          | 25       |
| Motor Activity: |    |    |    |    |    |    |    |             |          |
| Excited         | .. | .. | .. | .. | .. | .. | .. | 15          | 17       |
| Normal          | .. | .. | .. | .. | .. | .. | .. | 28          | 34       |
| Stuporose       | .. | .. | .. | .. | .. | .. | .. | 17          | 9        |
| Aggressiveness: |    |    |    |    |    |    |    |             |          |
| Aggressive      | .. | .. | .. | .. | .. | .. | .. | 32          | 24       |
| Normal          | .. | .. | .. | .. | .. | .. | .. | 9           | 19       |
| Withdrawn       | .. | .. | .. | .. | .. | .. | .. | 9           | 17       |
| Suicidal:       |    |    |    |    |    |    |    |             |          |
| Attempt         | .. | .. | .. | .. | .. | .. | .. | 3           | 3        |
| Ideas           | .. | .. | .. | .. | .. | .. | .. | 0           | 1        |
| Nil             | .. | .. | .. | .. | .. | .. | .. | 57          | 56       |
| Sleep:          |    |    |    |    |    |    |    |             |          |
| Insomnia        | .. | .. | .. | .. | .. | .. | .. | 10          | 6        |
| Normal          | .. | .. | .. | .. | .. | .. | .. | 50          | 54       |

## C.11

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Time Sampled Behaviour Record

(Behaviour exhibited in first 3 months after admission)

|                        | Leucotomies |    |    |    |    |    |    | Controls |
|------------------------|-------------|----|----|----|----|----|----|----------|
| Socialization:         |             |    |    |    |    |    |    |          |
| Mixing .. .. .         | ..          | .. | .. | .. | .. | .. | 7  | 15       |
| Solitary .. .. .       | ..          | .. | .. | .. | .. | .. | 53 | 45       |
| Attention:             |             |    |    |    |    |    |    |          |
| Alert .. .. .          | ..          | .. | .. | .. | .. | .. | 27 | 24       |
| Dull .. .. .           | ..          | .. | .. | .. | .. | .. | 33 | 36       |
| Speech:                |             |    |    |    |    |    |    |          |
| Garrulous .. .. .      | ..          | .. | .. | .. | .. | .. | 10 | 11       |
| Normal .. .. .         | ..          | .. | .. | .. | .. | .. | 31 | 31       |
| Mute .. .. .           | ..          | .. | .. | .. | .. | .. | 19 | 18       |
| Nutrition:             |             |    |    |    |    |    |    |          |
| Bulimia .. .. .        | ..          | .. | .. | .. | .. | .. | 2  | 0        |
| Normal .. .. .         | ..          | .. | .. | .. | .. | .. | 44 | 51       |
| Anorexia .. .. .       | ..          | .. | .. | .. | .. | .. | 12 | 9        |
| No information .. .. . | ..          | .. | .. | .. | .. | .. | 2  | 0        |

## C.12

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Time Sampled Behaviour Record

(Behaviour exhibited in first 3 months after admission)

|                              | Leucotomies |    |    |    |    |    |    | Controls |
|------------------------------|-------------|----|----|----|----|----|----|----------|
| Hospital work:               |             |    |    |    |    |    |    |          |
| Occupational therapy .. .. . | ..          | .. | .. | .. | .. | .. | 21 | 19       |
| Ward .. .. .                 | ..          | .. | .. | .. | .. | .. | 10 | 14       |
| Utility department .. .. .   | ..          | .. | .. | .. | .. | .. | 1  | 3        |
| Unemployed .. .. .           | ..          | .. | .. | .. | .. | .. | 23 | 18       |
| No information .. .. .       | ..          | .. | .. | .. | .. | .. | 5  | 6        |
| Mood:                        |             |    |    |    |    |    |    |          |
| Euphoric .. .. .             | ..          | .. | .. | .. | .. | .. | 8  | 7        |
| Normal .. .. .               | ..          | .. | .. | .. | .. | .. | 35 | 32       |
| Depressed .. .. .            | ..          | .. | .. | .. | .. | .. | 17 | 21       |
| Affect:                      |             |    |    |    |    |    |    |          |
| Apathy .. .. .               | ..          | .. | .. | .. | .. | .. | 26 | 34       |
| Normal .. .. .               | ..          | .. | .. | .. | .. | .. | 15 | 14       |
| Tension .. .. .              | ..          | .. | .. | .. | .. | .. | 17 | 12       |
| No information .. .. .       | ..          | .. | .. | .. | .. | .. | 2  | 0        |
| Awareness:                   |             |    |    |    |    |    |    |          |
| Confusion .. .. .            | ..          | .. | .. | .. | .. | .. | 30 | 31       |
| Sensorially clear .. .. .    | ..          | .. | .. | .. | .. | .. | 27 | 25       |
| No information .. .. .       | ..          | .. | .. | .. | .. | .. | 3  | 4        |

## C.13

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Time Sampled Behaviour Record

(Behaviour exhibited in first 3 months after admission)

|                            | Leucotomies |    |    |    |    |    |    | Controls |
|----------------------------|-------------|----|----|----|----|----|----|----------|
| Thought disorder:          |             |    |    |    |    |    |    |          |
| Present .. .. .            | ..          | .. | .. | .. | .. | .. | 56 | 49       |
| Absent .. .. .             | ..          | .. | .. | .. | .. | .. | 2  | 9        |
| No information .. .. .     | ..          | .. | .. | .. | .. | .. | 2  | 2        |
| Content:                   |             |    |    |    |    |    |    |          |
| Hallucinations .. .. .     | ..          | .. | .. | .. | .. | .. | 42 | 37       |
| Delusions .. .. .          | ..          | .. | .. | .. | .. | .. | 44 | 28       |
| Ideas of reference .. .. . | ..          | .. | .. | .. | .. | .. | 12 | 9        |
| "Dilapidation" .. .. .     | ..          | .. | .. | .. | .. | .. | 6  | 8        |
| Hypochondriasis .. .. .    | ..          | .. | .. | .. | .. | .. | 0  | 2        |

## C.14

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## General Results

|                                            |    |    |    | Single<br>Leuco-<br>tomies | Con-<br>trols | Multiple<br>Leuco-<br>tomies | Con-<br>trols | Total<br>Leuco-<br>tomies | Total<br>Con-<br>trols |
|--------------------------------------------|----|----|----|----------------------------|---------------|------------------------------|---------------|---------------------------|------------------------|
| Never Discharged*:                         |    |    |    |                            |               |                              |               |                           |                        |
| Men ..                                     | .. | .. | .. | 10                         | 14            | 1                            | 1             | 11                        | 15                     |
| Women ..                                   | .. | .. | .. | 24                         | 25            | 4                            | 5             | 28                        | 30                     |
|                                            |    |    |    | —                          | —             | —                            | —             | —                         | —                      |
| Total ..                                   | .. | .. | .. | 34                         | 39            | 5                            | 6             | 39                        | 45                     |
| Discharged and Re-admitted†:               |    |    |    |                            |               |                              |               |                           |                        |
| Men ..                                     | .. | .. | .. | 2                          | 0             | 0                            | 0             | 2                         | 0                      |
| Women ..                                   | .. | .. | .. | 6                          | 2             | 2                            | 1             | 8                         | 3                      |
|                                            |    |    |    | —                          | —             | —                            | —             | —                         | —                      |
| Total ..                                   | .. | .. | .. | 8                          | 2             | 2                            | 1             | 10                        | 3                      |
| Discharged and out of Runwell<br>Hospital: |    |    |    |                            |               |                              |               |                           |                        |
| Men ..                                     | .. | .. | .. | 2                          | 1             | 0                            | 0             | 2                         | 1                      |
| Women ..                                   | .. | .. | .. | 7                          | 8             | 1                            | 1             | 8                         | 9                      |
|                                            |    |    |    | —                          | —             | —                            | —             | —                         | —                      |
| Total ..                                   | .. | .. | .. | 9                          | 9             | 1                            | 1             | 10                        | 10                     |
| Transfers:                                 |    |    |    |                            |               |                              |               |                           |                        |
| Both sexes ..                              | .. | .. | .. | 1                          | 2             | 0                            | 0             | 1                         | 2                      |
|                                            |    |    |    | —                          | —             | —                            | —             | —                         | —                      |
| Grand Total ..                             | .. | .. | .. | 52                         | 52            | 8                            | 8             | 60                        | 60                     |
| Died:                                      |    |    |    |                            |               |                              |               |                           |                        |
| 1st admission* ..                          | .. | .. | .. | 1                          | 4             | 0                            | 1             | 1                         | 5                      |
| Subsequent admission† ..                   | .. | .. | .. | 1                          | 0             | 0                            | 0             | 1                         | 0                      |

## C.15

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Total Period Spent in Runwell Hospital since Operation Date

| Total Period |    |    | Leucotomies | Total | Controls | Total |
|--------------|----|----|-------------|-------|----------|-------|
| <1/12 ..     | .. | .. | 1           |       | 2        |       |
| 3/12 ..      | .. | .. | 1           |       | 2        |       |
| 6/12 ..      | .. | .. | 1           | 10    | 2        | 13    |
| 1 year ..    | .. | .. | 2           |       | 4        |       |
| 2 years ..   | .. | .. | 5           |       | 3        |       |
| 3 years ..   | .. | .. | 4           |       | 3        |       |
| 4 years ..   | .. | .. | 3           |       | 8        |       |
| 5 years ..   | .. | .. | 3           | 50    | 4        | 47    |
| 10 years ..  | .. | .. | 18          |       | 13       |       |
| +10 years .. | .. | .. | 22          |       | 19       |       |
|              |    |    |             | —     |          | —     |
| Total ..     | .. | .. |             | 60    |          | 60    |



## C.16

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Total Period Spent in Mental Hospitals since Operation Date

| Total Period    | Leucotomies | Total | Controls | Total |
|-----------------|-------------|-------|----------|-------|
| 1/12 .. .. .    | 1           |       | 2        |       |
| 3/12 .. .. .    | 0           |       | 2        |       |
| 6/12 .. .. .    | 0           | 7     | 2        | 12    |
| 1 year .. ..    | 2           |       | 2        |       |
| 2 years .. ..   | 4           |       | 4        |       |
| 3 years .. ..   | 3           |       | 3        |       |
| 4 years .. ..   | 3           |       | 7        |       |
| 5 years .. ..   | 4           | 53    | 5        | 48    |
| 10 years .. ..  | 18          |       | 13       |       |
| +10 years .. .. | 25          |       | 20       |       |
| Total .. ..     |             | 60    |          | 60    |

## C.17

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Post-operative Results During Further Stay in Runwell Hospital

| Treatment      | Leucotomies | Controls |
|----------------|-------------|----------|
| E.C.T. .. .. . | 23          | 17       |
| Leptazol .. .. | 9           | 6        |
| I.S.T. .. .. . | 0           | 0        |
| M.I. .. .. .   | 0           | 1        |
| P.N. .. .. .   | 0           | 3        |
| Drugs, etc. .. | 8           | 1        |

## C.18

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Post-operative Results During Further Stay in Runwell Hospital

| Health                              | Leucotomies | Controls | n=1<br>$\chi^2$ |
|-------------------------------------|-------------|----------|-----------------|
| Epileptic seizures .. .. .          | 11          | 0        | 9.9             |
| Chronic suppurative otitis media .. | 3           | 1        | 1.2             |
| Cellulitis .. .. .                  | 3           | 1        |                 |
| T.B. cervical glands .. .. .        | 1           | 0        |                 |
| Pulmonary abscess: bronchopneumonia | 1           | 1        |                 |
| P.T.B. .. .. .                      | 0           | 4        | 2.25            |
| Appendicitis .. .. .                | 1           | 1        |                 |
| Impetigo .. .. .                    | 0           | 1        |                 |
| Enuresis .. .. .                    | 1           | 0        |                 |
| Anaemia .. .. .                     | 2           | 3        |                 |
| Infestation—worms .. .. .           | 0           | 3        | 1.4             |
| Rectal prolapse .. .. .             | 1           | 0        |                 |
| Megacolon .. .. .                   | 0           | 1        |                 |
| Syncope .. .. .                     | 1           | 1        |                 |
| Herpes zoster .. .. .               | 1           | 0        |                 |
| Hypertension .. .. .                | 1           | 1        |                 |
| Glaucoma .. .. .                    | 1           | 0        |                 |
| Fibroids .. .. .                    | 0           | 1        |                 |
| Carcinoma .. .. .                   | 1           | 1        |                 |
| Osteoarthritis .. .. .              | 1           | 1        |                 |

## C.19

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Post-operative Results During Further Stay in Runwell Hospital

| Weight<br>Per cent. | Leucotomies |       |       |       |       | Controls |       |       |       |       |
|---------------------|-------------|-------|-------|-------|-------|----------|-------|-------|-------|-------|
|                     | 6/12        | 1     | 2     | 5     | 10    | 6/12     | 1     | 2     | 5     | 10    |
|                     | Year        | Years | Years | Years | Years | Year     | Years | Years | Years | Years |
| <80                 | 0           | 0     | 0     | 1     | 0     | 1        | 0     | 1     | 1     | 0     |
| -85                 | 0           | 0     | 1     | 0     | 1     | 0        | 2     | 1     | 0     | 1     |
| -90                 | 3           | 1     | 3     | 1     | 0     | 2        | 2     | 2     | 6     | 0     |
| -95                 | 4           | 4     | 6     | 2     | 1     | 3        | 3     | 9     | 3     | 1     |
| -100                | 8           | 8     | 5     | 6     | 2     | 20       | 19    | 16    | 5     | 5     |
| -105                | 11          | 11    | 6     | 3     | 4     | 17       | 11    | 3     | 6     | 5     |
| -110                | 9           | 7     | 3     | 6     | 2     | 7        | 8     | 9     | 5     | 0     |
| -115                | 7           | 10    | 10    | 6     | 4     | 1        | 4     | 5     | 3     | 1     |
| -120                | 6           | 3     | 5     | 3     | 1     | 2        | 0     | 1     | 3     | 1     |
| -125                | 2           | 5     | 3     | 3     | 1     | 0        | 1     | 2     | 0     | 0     |
| +125                | 3           | 3     | 7     | 7     | 7     | 0        | 1     | 0     | 4     | 5     |
| No information      | 7           | 8     | 11    | 22    | 37    | 8        | 9     | 11    | 24    | 41    |

Weight: Post-operative weight of each patient expressed as percentage of weight at date of operation:

$$\frac{\text{Post-operative weight (lbs.)}}{\text{Operation weight (lbs.)}} \times 100$$

## C.20

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

## Post-operative Results During Further Stay in Runwell Hospital

## Extract to Show Significant Gains in Weight

| Period After Operation   | Percentage Change | Leucotomies | Controls | n | $\chi^2$ | p      |
|--------------------------|-------------------|-------------|----------|---|----------|--------|
| 6/12 after operation     | <105              | 26          | 42       |   |          |        |
|                          | >105              | 27          | 10       | 2 | 13       | <0.001 |
|                          | No information    | 7           | 8        |   |          |        |
| 1 year after operation   | <105              | 24          | 37       |   |          |        |
|                          | >105              | 28          | 14       | 2 | 7.49     | <0.02  |
|                          | No information    | 8           | 9        |   |          |        |
| 2 years after operation  | <105              | 21          | 32       | 1 | 4.1      | <0.05  |
|                          | >105              | 28          | 17       | 2 | 4.97     | 0.1    |
|                          | No information    | 11          | 11       |   |          |        |
| 5 years after operation  | <105              | 13          | 21       | 1 | 3.4      | >0.05  |
|                          | >105              | 25          | 15       | 2 | 1.69     | 0.5    |
|                          | No information    | 22          | 24       |   |          |        |
| 10 years after operation | <105              | 8           | 12       | 1 | 2.32     | 0.3    |
|                          | >105              | 15          | 7        | 2 | 4.17     | 0.1    |
|                          | No information    | 37          | 41       |   |          |        |

## C.21

*Significant Weight Gain at 6/12 Post-operation in Relation to Discharge in 60 Schizophrenics Treated with Leucotomy*

|                                          | <105%<br>Weight at<br>Operation | >105%<br>Weight at<br>Operation | Total |
|------------------------------------------|---------------------------------|---------------------------------|-------|
| Discharged at some time from hospital .. | 10                              | 10                              | 20    |
| Never discharged .. ..                   | 16                              | 24                              | 40    |
| Total .. ..                              | 26                              | 34                              | 60    |
| n=1                                      | $\chi^2=0.2$                    | P=0.9                           |       |

## C.22

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

Results as far as Behaviour Rating is concerned in Survivors in Hospital (in June, 1957), Comparing 43 Leucotomy Patients with 38 Controls and Showing Change in Behaviour from Admission ("Before Operation") to June, 1957 ("After Operation"). Ratings in June, 1957 Estimated by Nursing Staff. Ratings on Admission from Case Records by Author

| Behaviour Rating | Leucotomies      |                 | Controls         |                 | For $n=1$<br>$\chi^2$ |
|------------------|------------------|-----------------|------------------|-----------------|-----------------------|
|                  | Before Operation | After Operation | Before Operation | After Operation |                       |
| Appearance:      |                  |                 |                  |                 |                       |
| Neat .. ..       | 20               | 17              | 21               | 15              | 0.2                   |
| Untidy .. ..     | 23               | 26              | 17               | 23              |                       |
| Motor Activity:  |                  |                 |                  |                 |                       |
| Excited .. ..    | 12               | 24              | 11               | 17              | 0.2                   |
| Normal .. ..     | 22               | 17              | 21               | 15              |                       |
| Stuporose .. ..  | 9                | 2               | 6                | 6               |                       |
| Aggressiveness:  |                  |                 |                  |                 |                       |
| Aggressive .. .. | 23               | 29              | 15               | 14              | 0.75                  |
| Normal .. ..     | 15               | 7               | 12               | 11              |                       |
| Withdrawn .. ..  | 5                | 7               | 11               | 13              |                       |
| Suicidal:        |                  |                 |                  |                 |                       |
| Attempt .. ..    | 1                | 0               | 1                | 0               |                       |
| Ideas .. ..      | 0                | 0               | 0                | 0               |                       |
| Nil .. ..        | 42               | 43              | 37               | 38              |                       |
| Socialization:   |                  |                 |                  |                 |                       |
| Mixing .. ..     | 5                | 11              | 6                | 5               | 0.8                   |
| Solitary .. ..   | 38               | 32              | 32               | 33              |                       |
| Attention:       |                  |                 |                  |                 |                       |
| Alert .. ..      | 20               | 18              | 13               | 10              |                       |
| Dull .. ..       | 23               | 25              | 25               | 28              |                       |

## C.23

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

| Behaviour Rating | Leucotomies      |                 | Controls         |                 | For $n=1$<br>$\chi^2$ |
|------------------|------------------|-----------------|------------------|-----------------|-----------------------|
|                  | Before Operation | After Operation | Before Operation | After Operation |                       |
| Speech:          |                  |                 |                  |                 |                       |
| Garrulous .. ..  | 8                | 14              | 6                | 9               |                       |
| Normal .. ..     | 23               | 22              | 19               | 18              |                       |
| Mute .. ..       | 12               | 7               | 13               | 11              |                       |
| Nutrition:       |                  |                 |                  |                 |                       |
| Bulimia .. ..    | 2                | 0               | 0                | 0               |                       |
| Normal .. ..     | 33               | 42              | 31               | 37              |                       |
| Anorexia .. ..   | 8                | 1               | 7                | 1               |                       |
| Sleep:           |                  |                 |                  |                 |                       |
| Insomnia .. ..   | 8                | 8               | 2                | 3               |                       |
| Normal .. ..     | 35               | 35              | 36               | 35              |                       |
| Hospital Work:   |                  |                 |                  |                 |                       |
| Occupational     |                  |                 |                  |                 |                       |
| Therapy .. ..    | 15               | 19              | 13               | 3               | 4.6                   |
| Ward .. ..       | 8                | 14              | 10               | 17              |                       |
| Utility .. ..    | 0                | 0               | 3                | 8               |                       |
| Unemployed .. .. | 18               | 10              | 11               | 10              | 0.2                   |
| No information   | 2                | 0               | 1                | 0               |                       |



## C.23 (continued)

| Behaviour<br>Rating | Leucotomies         |                    | Controls            |                    | For<br>n=1<br>$\chi^2$ |
|---------------------|---------------------|--------------------|---------------------|--------------------|------------------------|
|                     | Before<br>Operation | After<br>Operation | Before<br>Operation | After<br>Operation |                        |
| Mood:               |                     |                    |                     |                    |                        |
| Euphoric ..         | 8                   | 14                 | 5                   | 9                  |                        |
| Normal ..           | 23                  | 21                 | 18                  | 18                 |                        |
| Depressed ..        | 12                  | 8                  | 15                  | 11                 |                        |
| Affect:             |                     |                    |                     |                    |                        |
| Tension ..          | 11                  | 10                 | 5                   | 5                  |                        |
| Normal ..           | 22                  | 11                 | 8                   | 10                 |                        |
| Apathy ..           | 18                  | 22                 | 25                  | 23                 |                        |
| No information      | 2                   | 0                  | 0                   | 0                  |                        |

## C.24

*Sixty Pairs Matched for Sex, Age, Chronicity and Schizophrenia*

| Behaviour<br>Rating           | Leucotomies         |                    | Controls            |                    | For<br>n=1<br>$\chi^2$ |
|-------------------------------|---------------------|--------------------|---------------------|--------------------|------------------------|
|                               | Before<br>Operation | After<br>Operation | Before<br>Operation | After<br>Operation |                        |
| Awareness:                    |                     |                    |                     |                    |                        |
| Confusion ..                  | 21                  | 15                 | 20                  | 19                 |                        |
| Sensorially clear             | 19                  | 28                 | 18                  | 19                 |                        |
| No information                | 3                   | 0                  | 8                   | 0                  |                        |
| Thought Disorder:             |                     |                    |                     |                    |                        |
| Present ..                    | 42                  | 34                 | 31                  | 34                 | 0.6                    |
| Absent ..                     | 0                   | 9                  | 5                   | 4                  |                        |
| No information                | 1                   | 0                  | 2                   | 0                  |                        |
| Content:                      |                     |                    |                     |                    |                        |
| Hallucinations                | 31                  | 21                 | 27                  | 22                 | 0.1                    |
| Delusions ..                  | 35                  | 19                 | 17                  | 17                 | 1.3                    |
| Ideas of reference            | 5                   | 5                  | 5                   | 1                  |                        |
| Hypochondriasis               | 0                   | 2                  | 1                   | 0                  |                        |
| Phobias ..                    | 0                   | 2                  | 0                   | 2                  |                        |
| Obsessions and<br>compulsions | 0                   | 8                  | 0                   | 7                  |                        |

## C.25 AND C.26

*Nineteen Pairs Matched for Sex, Age on Admission, Length of Admission and Affective Disorder*

## C.25 Sex Distribution

| Sex       |    |    |    |    |    | Leucotomies | Controls |
|-----------|----|----|----|----|----|-------------|----------|
| Male ..   | .. | .. | .. | .. | .. | 2           | 2        |
| Female .. | .. | .. | .. | .. | .. | 17          | 17       |
| Total ..  | .. | .. | .. | .. | .. | 19          | 19       |

## C.26 Age Distribution

| Age on Admission |    |    |    |    |    | Leucotomies | Controls |
|------------------|----|----|----|----|----|-------------|----------|
| -40 ..           | .. | .. | .. | .. | .. | 2           | 4        |
| -50 ..           | .. | .. | .. | .. | .. | 0           | 1        |
| -60 ..           | .. | .. | .. | .. | .. | 12          | 10       |
| +60 ..           | .. | .. | .. | .. | .. | 5           | 4        |
| Total ..         | .. | .. | .. | .. | .. | 19          | 19       |

## C.27

*Nineteen Pairs Matched for Sex, Age on Admission, Length of Admission and Affective Disorder*

## Length of Admission to Operation Date

| Length of Admission |    |    |    |    |    | Leucotomies |    | Controls |    |
|---------------------|----|----|----|----|----|-------------|----|----------|----|
| -1/12               | .. | .. | .. | .. | .. | 8           |    | 7        |    |
| -3/12               | .. | .. | .. | .. | .. | 1           |    | 3        |    |
| -6/12               | .. | .. | .. | .. | .. | 1           | 15 | 0        | 13 |
| -1 year             | .. | .. | .. | .. | .. | 3           |    | 1        |    |
| -2 years            | .. | .. | .. | .. | .. | 2           |    | 2        |    |
| -3 years            | .. | .. | .. | .. | .. | 2           |    | 3        |    |
| -4 years            | .. | .. | .. | .. | .. | 1           |    | 2        |    |
| -5 years            | .. | .. | .. | .. | .. | 0           | 4  | 1        | 6  |
| -10 years           | .. | .. | .. | .. | .. | 0           |    | 0        |    |
| +10 years           | .. | .. | .. | .. | .. | 1           |    | 0        |    |
| Total               | .. | .. | .. | .. | .. | 19          | 19 | 19       | 19 |

## C.28

*Nineteen Pairs Matched for Sex, Age on Admission, Length of Admission and Affective Disorder Results*

| Results                           |    |    |    |    |    | Leucotomies |     | Controls |     |
|-----------------------------------|----|----|----|----|----|-------------|-----|----------|-----|
| Never discharged                  | .. | .. | .. | .. | .. | 5           |     | 7        |     |
| (Died during 1st admission)       | .. | .. | .. | .. | .. |             | (2) |          | (3) |
| Discharged                        | .. | .. | .. | .. | .. | 11          |     | 12       |     |
| Re-admitted                       | .. | .. | .. | .. | .. |             | 5   |          | 5   |
| Not re-admitted                   | .. | .. | .. | .. | .. |             | 6   |          | 7   |
| (Died on subsequent re-admission) | .. | .. | .. | .. | .. |             | (1) |          | (0) |
| Transferred                       | .. | .. | .. | .. | .. | 3           |     | 0        |     |
| Total                             | .. | .. | .. | .. | .. | 19          |     | 19       |     |

## C.29 AND C.30

*Twelve Pairs Matched for Sex, Age on Admission, Length of Admission and Depression*

## C.29 Sex Distribution

| Sex    |    |    |    |    |    | Leucotomies |  | Controls |  |
|--------|----|----|----|----|----|-------------|--|----------|--|
| Male   | .. | .. | .. | .. | .. | 1           |  | 1        |  |
| Female | .. | .. | .. | .. | .. | 11          |  | 11       |  |
| Total  | .. | .. | .. | .. | .. | 12          |  | 12       |  |

## C.30 Age Distribution

| Age on Admission |    |    |    |    |    | Leucotomies |  | Controls |  |
|------------------|----|----|----|----|----|-------------|--|----------|--|
| -40              | .. | .. | .. | .. | .. | 0           |  | 2        |  |
| -50              | .. | .. | .. | .. | .. | 2           |  | 1        |  |
| -60              | .. | .. | .. | .. | .. | 7           |  | 6        |  |
| +60              | .. | .. | .. | .. | .. | 3           |  | 3        |  |
| Total            | .. | .. | .. | .. | .. | 12          |  | 12       |  |

## C.31

*Twelve Pairs Matched for Sex, Age on Admission, Length of Admission and Depression*

| Length of Admission to Operation Date |    |    |    |    |    | Leucotomies |    | Controls |    |
|---------------------------------------|----|----|----|----|----|-------------|----|----------|----|
| Length of Admission                   |    |    |    |    |    |             |    |          |    |
| -1/12                                 | .. | .. | .. | .. | .. | 6           |    | 5        |    |
| -3/12                                 | .. | .. | .. | .. | .. | 1           |    | 3        |    |
| -6/12                                 | .. | .. | .. | .. | .. | 1           | 10 | 0        | 11 |
| -1 year                               | .. | .. | .. | .. | .. | 1           |    | 1        |    |
| -2 years                              | .. | .. | .. | .. | .. | 1           |    | 2        |    |
| -3 years                              | .. | .. | .. | .. | .. | 2           |    | 0        |    |
| -4 years                              | .. | .. | .. | .. | .. | 0           | 2  | 1        | 1  |
| Total                                 | .. | .. | .. | .. | .. | 12          | 12 | 12       | 12 |

## C.32

*Twelve Pairs Matched for Sex, Age on Admission, Length of Admission and Depression Results*

| Results                           |    |    |    |    |    | Leucotomies |     | Controls |     |
|-----------------------------------|----|----|----|----|----|-------------|-----|----------|-----|
| Never discharged                  | .. | .. | .. | .. | .. | 3           |     | 3        |     |
| (Died during 1st admission)       | .. | .. | .. | .. | .. |             | (1) |          | (1) |
| Discharged                        | .. | .. | .. | .. | .. | 9           |     | 9        |     |
| Re-admitted                       | .. | .. | .. | .. | .. |             | 4   |          | 2   |
| Not re-admitted                   | .. | .. | .. | .. | .. |             | 5   |          | 7   |
| (Died on subsequent re-admission) | .. | .. | .. | .. | .. |             | (1) |          |     |
| Transferred                       | .. | .. | .. | .. | .. | 0           |     | 0        |     |
| Total                             | .. | .. | .. | .. | .. | 12          |     | 12       |     |

## SUMMARY AND CONCLUSIONS

A. (i) Groups matched for schizophrenia, sex, age on admission and length of admission are also shown to be comparable as far as:

1. Total length of previous admissions to Runwell Hospital.
2. Total length of previous admissions to other mental hospitals.
3. Civil state (single, married, etc.).
4. Occupational record as far as stability is concerned.
5. Family history of mental illness and suicide.
6. Type of school attended and progress.
7. Heterosexual attainment—a history of heterosexual friendships, an engagement, etc.
8. Intemperate habits.
9. Personality types.
10. Age at onset of first symptoms.
11. Type of onset of symptoms—acuteness, etc.
12. Response to electroplexy.
13. Number of remissions in the illness.
14. Occlusive index.
15. Immobility index.

16. Mean weight (in pounds) on admission and at operation date.

17. All physical treatments (apart from prolonged narcosis) used prior to operation date.

(ii) A behaviour rating scale also showed the leucotomy and control groups to be comparable as far as 15 items of behaviour were concerned.

(iii) The therapeutic results of leucotomy in schizophrenia comparing treatment and control groups matched as above are shown as temporary.

(iv) The incidence of epilepsy after leucotomy is markedly higher than in the control group.

(v) The gain in weight following leucotomy appears to disappear about two years post-operatively and is not an indication of prognosis.

(vi) Leucotomy does not significantly improve hospital behaviour in schizophrenia as measured by a behaviour scale, comparing periods before and after operation in leucotomy and control groups.

B. Leucotomy does not appear to benefit affective disorders and in particular depression, when groups are compared, matched for diagnosis, sex, age on admission and chronicity.



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# MENTAL DISORDER IN RURAL GHANA

By

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## PREFACE

THIS paper summarizes the main findings of two years' ethno-psychiatric field-work carried out in N.W. Ashanti throughout 1956 and 1957, and later to be published in full detail.

The picture surrounding the rural field-worker is essentially different from that seen by psychiatrists in mental hospitals. In rural districts only homicidal patients are ever referred to a mental hospital, and then only from the police-magistrate's court. All other mental illness is regarded as supernaturally determined and hence outside the province of European medicine.

## SOURCES OF CASES

The chronic cases were Ashanti people, justly deemed "mad", and were sought out by the writer and examined in their own homes with the co-operation of various chiefs, village headmen and elders around the writer's base.

The new cases, comprising a variety of mental illnesses, were found among the pilgrim supplicants at some 28 shrines of native deities. These pilgrims are by no means all Ashantis, but come from far and wide, so offering a fair sample of all the Akan tribes of Ghana.

## THE SHRINES AND THEIR WORK

Very few of the shrines are ancient, but have sprung up in striking response to a sense of insecurity which can be correlated with the growth of the cocoa industry. Ghana cocoa is all grown by African farmers, mostly illiterate non-Christians, whose cocoa-farming constitutes a hazardous but financially rewarding venture into individual effort and a breakaway from the old tribal security based on traditional roles, kinship solidarity and mutual obligation.

At the turn of the century the country was exporting annually about 400 tons of cocoa, in 1910 nearly 21,000 tons, and in 1925 nearly 206,000 tons. The earliest of the modern shrines appear to have been established between 1910 and 1920 and the number is still rapidly increasing. Of the twenty-eight shrines that came within the writer's ambit, only three were ancient; three were established between 1914 and 1919, the influenza pandemic which exterminated whole villages in Ashanti being a datum-line specifically mentioned by informants; sixteen were set up less than ten years ago; six were newly established during the writer's two years' sojourn in the district.

Mentally ill people comprise only a very small proportion of the pilgrims who flock to these shrines. The great majority are healthy people supplicating for "protection". Financially successful men are full of fear lest envious kinsmen should, by means of bad magic or witchcraft, bring about their ruin.

Unsuccessful men are convinced that envious malice is the cause of their failure. Thus, a strikingly "paranoid" attitude is normal. Healthy intelligent Africans have some insight into the prevalent distrust and envy and often refer to it spontaneously as one of the weaknesses of "us black men". As might be expected, psychotics commonly retain, much accentuated, this trait.

The typical pilgrim comes annually to the shrine, asks the deity for a year's protection and promises a thank-offering of a sheep and a bottle of rum at the end of the year. The deity's protection and blessing is granted conditionally on the supplicant's keeping prescribed rules of ethical conduct. He must not steal, commit adultery, bear false witness nor curse another person. And above all he must neither possess bad talismans, make bad magic against others, nor engage in witchcraft. If he breaks any of these rules the deity will first "catch hold" of him and then, if he does not promptly confess and obtain pardon, will swiftly kill him or, alternatively, smite him with permanent madness.

Many illnesses, both physical and mental, are thus intensified by an iatrogenic element of guilt and fear. The patient believes himself "caught hold of" and presents a wild psychotic picture of frenzied terror. The guilt-feelings may be well founded—the patient may, in fact, have transgressed the deity's rules—but in the case of depressions the patient claims, in classically depressive fashion, to have done immense harm by means of witchcraft. In both cases the ritual of confession and absolution at the shrine extinguishes the frenzy by filtering off the fear, and, except in primary depressions, washes away the sense of guilt.

Witchcraft, according to the accepted dogma, differs from cursing and bad magic-making in that it involves neither concrete apparatus nor ritual acts, but is a mysterious destructive influence exerted by the witch, usually against her will and without her knowledge. It thus meets, above all else, every depressive's need to steep himself in irrational self-reproach, and she denounces herself as an unspeakably wicked witch responsible for all the surrounding misfortunes and deaths.

Thus do the paranoid and the depressive fulfil complementary social functions. The one is seeking someone to blame for his failure or misfortune, the other is craving to accept unlimited guilt.

#### THE ACUTE TRANSIENT PSYCHOSES

These fear-and-guilt frenzies, already mentioned in passing, are among the commonest and also the most striking of the new cases for which the shrines are virtually admission wards.

These mental states are occasionally precipitated by physical illness, particularly such fevers as malaria, influenza or pneumonia. The patient feels unwell, thinks the deity has laid a hand on him for some offence committed in a heedless moment and disregarded, becomes frightened and then frenzied. But fear in pure culture is often observed. The following is an example.

A young pregnant woman, under the protection of a shrine deity, developed a severe toxæmia, said she had sinned, was taken to the shrine and died in an eclamptic fit before she could confess. Her uncle in another village heard the news, was seized by an abandonment of grief, grabbed a stick and beat the ground, denouncing the deity who had killed his favourite niece. When his rage was spent he began to have misgivings. Would the deity kill him for his arrogant and impious outburst? He went to bed but could not



sleep. He began to feel pains all over. His skin "burnt like fire". He rushed into the yard where all his friends tried in vain to soothe him. His agitation grew. By morning he was raving mad, talking gibberish, shouting, fighting, tearing off his clothes and rushing away into the bush. His friends brought him, bound hand and foot, to the shrine. He himself could make no statement but grasped that his friends made one for him and that the deity pronounced pardon. He calmed down and within a few days had completely recovered, though remembering nothing that occurred after he lay sleepless in his room.

Most of the frenzied guilt-and-fear patients do not so promptly reach the shrine, and by the time they arrive they are quieter but have become indistinguishable from classical schizophrenics. Such a patient is inaccessible, hallucinated, smiling, giggling, posturing, crawling, dancing, singing, tearing off his clothes, eating faeces, saying that there are trees in his belly and animals inside his head. However, he is led to the shrine and within a week is well. If the causative guilt was only imaginary, depressive guilt, the fear is filtered off leaving only a straightforward depression.

These short-lived, guilt-and-fear psychoses might be dismissed as purely iatrogenic with the remark, "no threatening deity, no fear-psychosis", were it not for one interesting finding, that is, the histories and follow-ups—which it is possible to obtain only when one can see the patients in their own homes or see them returning with their yearly reports to the shrines—reveal that the potential schizophrenic is particularly vulnerable to the guilt-and-fear psychosis. One example may be cited:

A young blacksmith, his apprenticeship just completed, came to the shrine asking that his new venture as an independent worker might prosper. It did and he duly brought a sheep as thank-offering. Later, becoming more avaricious, he purchased from a bad medicine-man a talisman to enrich himself at the expense of his kinsmen. This was against the deity's rules and the blacksmith developed misgivings, followed by an acute, frenzied guilt-and-fear psychosis. He was brought in fetters to the shrine, where he quickly recovered. He then asked permission to stay in the deity's village and work there as a blacksmith. This was granted and he settled down as a highly skilled and industrious worker, in which role the writer first knew him. However, after about a year he started neglecting his work, hiding his tools in the bush, taking his forge to pieces and quickly developed a frank but unobtrusive schizophrenia.

Mental hospital workers in other parts of Africa (Margetts (6), Smartt (8)) have observed similar transient psychoses and frenzied anxieties. These cases, brought to the hospital because of their unmanageable nature, are quickly discharged and lost sight of, no follow-ups being possible. It may well be, however, that many such cases, like those which the present writer had, as a field-worker, the unique opportunity of following up, subsequently develop an unobtrusive schizophrenia, quite disabling to the patient but not sufficiently disturbing to others to impel them to seek help in imposing restraint.

#### DEPRESSION

This is the commonest mental illness of rural women and all such patients come to the shrines with spontaneous self-accusations of witchcraft—that is, of having wrought harm without concrete act or conscious will (Field (2)).

The older age-group is characterized by well-defined classical involutional depression with agitation. The patients are conscientious women of good personality who have worked hard and launched a fleet of well brought-up children. Many of them have paid for their children's schooling with money earned by diligent trading, market-gardening or cocoa-farming. Asked to describe the onset of their symptoms they use the phrases familiar in the admission wards of European mental hospitals: "I became useless. I couldn't do any work but neither could I sit still and rest. At night I couldn't sleep because my mind was restless and I often got up and walked about." Then they add, "Soon I knew that I was no good and had become a witch. I have done so much evil that I ought to be killed."

In the depression of younger women there is often considerable convergence of causes. Vast numbers of ordinary rural people have subclinical vitamin deficiencies which become acute when any unusual call, such as pregnancy or debilitating illness, is made upon vitamin reserves. As is well known, the classical features of beri-beri, pellagra, kwashiorkor and scurvy include mental symptoms. Furthermore, hookworm and malaria are able to produce severe anaemia. Many rural women have a long string of pregnancies without any cessation of lactation over a number of years, and finally a point is reached when childbirth, particularly if accompanied by any sepsis, precipitates a depression. If the new-born child is sickly and dies, there is an added element of reactive depression and the patient, tormented by irrational guilt, says that it was she herself who, by witchcraft, killed it.

#### OBSESSIVE-COMPULSIVE PSYCHOSIS

It has been widely held that this illness is unknown among unsophisticated Africans. (Carrothers (1)). It is certainly uncommon but the writer encountered two major cases among illiterate rural supplicants at shrines.

One was a young woman, unhappily married and estranged from her kin. She was beset, to her own horrified distress, by urges to seize a cutlass and kill her children. The other was an adolescent girl who, in times of stress, unceasingly swept the courtyard, tidied the village street, and shook imaginary lice out of her well-washed clothing. Sometimes, she rose in the night and swept till forcibly restrained.

The English obsessive, when in depression and self-denigration, tends to postulate *concrete* agents—disease-germs and vermin—rather than defects of character as constituting her menace to others. Several patients with delusions that they were disseminating plagues of lice have been met at shrines.

The rarity of the obsessive personality is reflected in all social activities and institutions. Among magical procedures, the spell—defined as a recitation which must be meticulously word-perfect in order to work—is nowhere found. Nor, in African social organization, are there any traces of that mental rigidity which could conceive and sustain so fantastic a social fabric as the Indian caste system.

#### RELATION BETWEEN SCHIZOPHRENIA AND BAD MAGIC

It has been mentioned that one of the activities specifically forbidden to those under the protection of shrine deities is the making of bad magic or "medicine" against others, that disobedience to this injunction frequently brings the offender to the shrine in a psychotic frenzy and that classical schizophrenia often eventually follows. Experience has further taught the writer

that secret ritual with "bad medicines" and other magical apparatus often ushers in a frank schizophrenia without any inaugural episode of transient frenzy. The making of secret bad magic against others is, in fact, a schizoid type of aggression as distinct from a healthy, quarrelsome type of aggression. Into the same class of schizoid personality would have fallen a celebrant of the mediaeval Black Mass, performing his sinister rites in solitude at midnight. Of many a long-standing chronic schizophrenic is it said, putting the cart before the horse, "He became mad because he made bad medicine. The *suman* (apparatus) were found hidden in his room." This does not imply that *only* potential schizophrenics make bad magic against others but merely that this type of aggression is particularly favoured by schizophrenics.

#### THE INCIDENCE OF CHRONIC SCHIZOPHRENIA

In twelve Ashanti villages representing (according to the 1948 census) a population totalling 4,283, all the discoverable schizophrenics were examined and their histories recorded. These totalled forty-one. There may have been others not discovered, and others again who died from lack of skilled nursing. The residual dementias and behaviour disorders of late-treated trypanosomiasis and the epileptics were not, of course, included. Nor were "strangers"—e.g., non-Ashanti migrant cocoa-farmers and labourers from other districts, though some had developed indubitable schizophrenia and had not gone home. Excluded also from this survey were those cases which left any possibility, in the examiner's mind, that they might be mental defectives.

#### RELATION BETWEEN SCHIZOPHRENIA AND EDUCATION

Whereas the incidence of literacy among the overall population of Ghana is usually estimated at 10 per cent., the incidence of literacy among the 95 combined new and chronic cases of schizophrenia examined by the present writer, was found to be above 40 per cent.

In England, Ghana and Nigeria, at the present time, concern is being expressed about the large number of young Africans who go to Britain for study-courses and there suffer mental breakdown. But it is not appreciated how high is the breakdown rate among young literates of only primary-school standard who remain in their own country in their own homes. They are less conspicuous than those who break down in Britain but they are probably no fewer.

The reason for the literate breakdown appears, in rural Ashanti, not far to seek. In any village or small country town, on any morning of the week, are to be seen numerous able-bodied men sitting under trees drinking palm-wine or playing draughts while other idlers look on. They are all farmers, but only during planting, harvesting and weeding need they do any active work, and even then, if they feel disinclined, some kinsman or wife will usually take over. No demands are made on most men in the way of regularity or punctuality. Simple schizophrenia may thus go unnoticed. Other potential schizophrenics may never meet any stress severe enough to precipitate an attack. The literate's life is, however, more exacting. Its demands begin before the adolescent leaves school. Often the young schizophrenic simply gives up going to school saying that he does not want to continue. Teachers are well aware of this leakage of adolescents from schools. But perhaps the young schizophrenic scrapes through his primary-school leaving examination and



takes a job. He does not keep it long, and sooner or later he drifts home again, unemployed and unemployable, a permanent loafer, but not conspicuous, accepted with little resentment by his easy-going kinsmen.

There are three programmes now being mooted in the new and eagerly go-ahead Ghana: universal literacy, industrialization, and compulsory non-military training-camps for unemployed literates. Any one of these schemes put resolutely into operation could probably provoke a startling outburst of acute schizophrenia. Widespread opportunity animates not only latent talent—the village Hampden and the erstwhile mute inglorious Milton—but the latent schizophrenic.

#### RELATION BETWEEN SCHIZOPHRENIA AND IN-BREEDING

The Ashanti and other Akan peoples of Ghana have for many generations practised that form of first-cousin marriage whereby a man gives his daughter as bride to his sister's son and waives the marriage-fee, which would be demanded from a non-kinsman.

Among the parents of 95 undoubted schizophrenics it was found that the incidence of cousin marriage was 40 per cent., whereas among the general population (taking 1,200 marriages) the incidence of cousin marriage was only 19 per cent.

This correlation does not necessarily imply that cousin marriage is the operative genetic factor. A young person of schizoid personality, lacking self-assertion and "drive", is of the type to accept passively the marriage partner offered by senior kinsmen. The more spirited and enterprising seek the stimulus of new contacts. The same principle of passive acceptance of tradition by schizoid personalities would equally apply if the favoured tradition had been to marry, say, someone born on the same day of the week or someone who had never had chicken-pox.

#### DREAMS

Dreams are regarded as highly important and when vivid or frightening give the dreamer great anxiety till a satisfying interpretation is found. Such interpretation is a part of the work of the shrines.

Different persons in similar situations often dream identical stereotyped dreams. For instance, people in fear of retribution for sin commonly dream that the deity, in the guise of a long-haired priest, is chasing them with a club and sometimes knocks them down.

Most dreams are of a straightforward type and are simple allegories based on everyday metaphor. The hill difficulty, the slough of despond, the lion in the path, the traveller on the road of life, the crossing of the river of death, have the same significance in dreams as in universal speech. Symbols based on physical similarity are seldom used. Thus, a house is a symbol of security ("as safe as houses"), rather than an ingeniously disguised uterus. A "snake in the grass" is more likely to symbolize a smooth-tongued, but cocoa-stealing neighbour than unconscious sexual yearnings.

The simple parable is, to the unsophisticated mind, not only a highly acceptable aid to understanding ("and without a parable spake he not unto them") but is the commonest mode of summing up, in dreams, the dreamer's current situation. Seldom does any deeper mental layer appear to be tapped. An example of this parabolic symbolism, used to enunciate an anxiety-

charged but fully manifest situation, was provided by a young woman who came to a shrine worried by a dream in which her aunt, with whom she was on genuinely friendly terms, had offered her black toadstools to eat. She tasted one, thought it poisonous, and rejected the others. She and the aunt came together to the shrine, both in anxiety because they both wondered whether the dream signified that the older woman was a witch and was trying to impart the power of witchcraft to her kinswoman. Both were sufficiently depressed to be ready to accept a witch's role. The shrine deity confirmed their interpretation and prescribed a course of ritual bathing at the shrine to purify them. They carried out the treatment but remained depressed and anxious. Later they divulged their domestic circumstances. The younger woman was married to an alcoholic who was fighting his addiction and had even become a Mohammedan to lessen temptation. But his wife lived in secret dread of his relapse. The older woman had a son who was a confirmed and degraded drunkard. The significance of the dream then became clear: the young woman was in fear of sharing her aunt's black and bitter lot.

### HYSTERICAL DISSOCIATION

This phenomenon, the spectacular nature of which has, of late years, made it a favourite topic of popular travel books and motion-films, rarely presents in Ghana as a mental illness. Its exponents are, among the Ashanti, mainly priests, and among the Ga'-Adangme tribes, not priests but women auxiliaries (*woyei*) whose duty and delight it is at big religious festivals to act as possessed mediums and mouthpieces of the gods.

Only during the early training period of new mediums is their behaviour in any way unpredictable or fraught with danger to themselves. (Field (3) (5)). Later, with training and conditioning, their behaviour becomes automatic and controlled according to traditional ritual.

The possession fit is essentially an excitement, seldom of more than an hour's duration. It is usually preceded by a state of dreamy, dazed inertness, during which the medium sits with bowed head, inaccessible and seemingly oppressed. The skin is cold and clammy. This, after a few minutes, suddenly gives way to motor excitement, sometimes with furious dancing and wild activity and usually a mask-like face. In due time the excitement stops abruptly, leaving the medium with an amnesia for the incident and in a state of weariness or exhaustion proportionate to the amount of physical energy expended.

Though technically the possessed state is one of hysterical dissociation its typical exponents are not hysterical personalities and, far from being mal-adjusted, play a valued role, behaving, in the intervals of humdrum life, as ordinary, inconspicuous, dignified members of their community.

The technique of dissociated excitement is not usually, as in some other parts of Africa (Pidoux (7)), employed therapeutically except among the Ga who use it to expel bad "*gbesi*" (Field (4)), and among those African Christians who have broken away from the European styles of worship and have founded their own Christian cults. The latter communities claim, perhaps with good foundation, to worship in the style of the earliest Christians. Members of their congregations, both healthy and sick, become possessed in the indigenous manner, but, in their belief, by the Holy Ghost. Sometimes almost a whole congregation may be Pentacostally affected. The possessed participants describe a long-lasting aftermath of peaceful euphoria following this

dissociation, and certainly most members of these communities appear happier, more generous and harder-working than their compatriots.

#### ROLE OF MENTAL DISORDER IN THE HISTORY OF BELIEF

There can be little doubt that the depressive's fantastic self-accusations, in modern Europe taken as one criterion of illness, but in rural Africa and mediaeval Europe taken as statements of fact, not only keep alive in present-day Ghana the whole ideology of malevolent witchcraft, but quite probably, in the distant past, begat it.

By a similar postulate, many of these schizophrenics who, by retaining their accessibility in a setting of clear consciousness, escaped popular dismissal as madmen, probably had a profound influence on the tenets of primitive belief.

The predilection of the incipient schizophrenic for ritual with traditionally magical objects has already been mentioned. It should now be added that a well-preserved schizophrenic frequently produces, sometimes to his own distress, *original* fantasies in which concrete objects and the manipulation of these have, for him, a mysterious association with persons and events. One well-preserved and outwardly normal woman was plagued with a great variety of such fantasies: she confessed at the shrine—and was naively believed—that her spirit (*sunsum*) actually carried out these rites. She said, for instance, that she had an invisible bottle in the roof of her house and when, in spirit, she corked it, she caused all women in labour to be obstructed: when she uncorked it they promptly delivered.

It may well be that many traditional magical procedures were thus invented by schizophrenics of sufficiently normal aspect to make their statements acceptable to their fellow-men. The so-called "primitive mind" may thus be merely the credulous mind, able to accept—albeit with awe, wonder, fear and, above all, frank incomprehension—more bizarre notions than would have occurred to itself.

This gives a new slant to such "primitive" ideas as lycanthropy and to the vexed question of the origin of animal totemism.

Regarding the latter, the present writer can recall instances, not only in rural Africa but in modern England, of well-presenting schizophrenics who felt that certain animals had a special significance for them. One such patient, a London woman, said that when she walked in the parks all the birds seemed to be trying to bring her mysterious messages. Another English patient said that the thrushes in the hospital grounds seemed to be, in some strange way, identified with his wife and the sparrows with his children.

It is probably not correct to say that such patients "revert to primitive modes of thought". It seems more likely that schizophrenic modes of thought are specific to schizophrenia and are independent of cultural background. It is their assessment and acceptance by others that is culturally determined.

#### SUMMARY

In rural Ghana new shrines continue to be founded in response to a search for security begun about 40 years ago.

The commonest mental illnesses seen at these shrines are depression, acute transient fear-psychosis, and schizophrenia. Obsessive-compulsive states are rare but do occur.

Potential schizophrenics are specially vulnerable to transient fear-psychosis. The making of bad magic against others is a schizoid type of aggression especially prone to occur in developing schizophrenia.



The incidence of chronic schizophrenia in a rural population of 4,000 was found to be about 1 per cent.

The incidence of literacy among schizophrenics was found to be about 40 per cent. as against 10 per cent. among the general population.

The incidence of first-cousin marriage among the parents of schizophrenics was found to be about 40 per cent. as against 19 per cent. among the general population.

Among supplicants at shrines, dreams are deemed highly important. Persons in similar anxiety-charged situations often have identical dreams of traditional content. Most dreams sum up the dreamer's overt situation in parabolic metaphor.

Hysterical dissociation (spirit possession) is part of the technique of priests, these being well adjusted, non-hysterical personalities. It is used therapeutically by some African-controlled Christian communities.

It is postulated that some kinds of magical ritual, animal totemism, and the maleficent powers attributed to witches were originated, historically, by schizophrenics and depressives.

#### ACKNOWLEDGMENT

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# TREATMENT OF ANXIETY STATES

## I. THE EFFECTS OF SUGGESTION ON THE SYMPTOMS OF ANXIETY STATES

By

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THE increasing importance of properly controlled drug trials in modern medicine has shown the need for further study of the "placebo response" and the effects of "suggestion", particularly in the evaluation of the results of treatment of the psychoneuroses. Much of the work on the response to placebos has been done on their deleterious side-effects, *i.e.*, the production of symptoms of various kinds, but some recent investigations have clearly demonstrated the amelioration of symptoms by the administration of placebo.

Glaser (1953), in an investigation of the efficacy and side-effects of various alleged remedies for sea-sickness, found that experimental procedures alone, such as filling in questionnaires or taking inert tablets, could give rise to symptoms in his student and Army subjects. These responses progressively diminished when the experimental procedures were repeated at weekly intervals and it would appear that the responses varied according to the interest of the subjects in the experiment. This work illustrates the fact that the human subject responds to the total situation in which he is placed, one facet of which may produce a favourable or unfavourable milieu for a favourable or unfavourable response to a placebo, *e.g.*, the interest and sympathy of the physician may create a suitable background for the beneficial placebo response, or *vice versa*.

In a consideration of the "placebo response", Tibbetts and Hawkins (1956) referred to two investigations (1956a, 1956b) they had carried out on groups of psychoneurotic patients. In the first they compared the effects of inhalation of carbon dioxide with compressed air; and in the second they compared the effect of injections of acetyl-choline with sterile water. In each case, approximately half of the patients improved irrespective of whether the pharmacologically active or inert substance was given. Those deriving benefit from the inactive agents were regarded as "placebo reactors", a concept introduced by Beecher *et al.* (1953) and further studied by Lasagna *et al.* (1954). Further scrutiny of the symptomatology of Tibbetts and Hawkins' 41 patients showed a consistent tendency for patients with "unelaborated anxiety" to respond more favourably to placebo administered under the conditions of their trials. This response was much less in patients suffering from hysterical conversion.

It is often asserted that in the treatment of neurosis, explanation and reassurance may be of great value, but there is a marked paucity of reports of enquiries on this point. One reason for this may lie in the manifest difficulty of assessing accurately the patient's condition, "global" assessments being notoriously unsatisfactory for this purpose.

### PRESENT ENQUIRY

As a preliminary to a recent enquiry into the treatment of anxiety states an attempt was made to investigate further the effects of "suggestion". The trial population consisted of 34 patients, 17 men and 17 women suffering from anxiety states of less than 4 years' duration without evidence of other psychiatric disorders; no patient showed evidence of hysterical conversion. Their ages ranged from 22-62 years, with a mean age of 38·7 years.

Initially each patient was given a full psychiatric interview, including some discussion, explanation and reassurance when appropriate; a rating was made on a scale of 13 variables covering various psychic and somatic anxiety symptoms (Hamilton, 1958). Each patient was then given a prescription for one inert tablet, *t.d.s.* for two weeks, being interviewed again after one week and again after the second week. At the third interview an independent rating was made by another psychiatrist as well as by the original physician. Inter-physician correlation between the symptom ratings, giving a measure of their reliability, had a mean of +0·89. The rating at the third interview was subtracted from that at the first to give a score representing improvement, and the improvement in the total score for each patient was thus obtained. The mean improvement in total score for the 34 patients is 1·91 points which is statistically highly significant ( $P < 0\cdot01$ ).

Consideration of the scores on individual symptoms shows a general improvement for the whole group of patients, apart from the genito-urinary symptoms, which remained unchanged, and autonomic disturbances, which showed a mean worsening of 0·03 points (not significant). The symptoms showing most improvement were:

|              |      |        |      |              |              |
|--------------|------|--------|------|--------------|--------------|
| Anxious mood | 0·35 | points | mean | improvement, | $P=0\cdot01$ |
| Insomnia     | 0·24 | "      | "    | "            | $P=0\cdot02$ |
| Tension      | 0·24 | "      | "    | "            | $P=0\cdot05$ |

An improvement of one point means a shift from a severe symptom to a moderate one, from moderate to mild, or from mild to absent. A mean shift of a third of a point means that one patient in three improved by one point.

After the initial fortnight, 12 of the original total of 34 patients went on receiving inert tablets for a further period of 3 weeks, when symptoms were again assessed by the same two psychiatrists who had assessed them before. It is therefore possible to measure the changes in symptom-scoring occurring during this further period: a mean improvement of almost 3 points for the 12 patients was noted, and this is significant statistically ( $0\cdot05 > P > 0\cdot02$ ). When the individual symptoms are examined, those with most improvement are:

|                          |      |        |             |                             |
|--------------------------|------|--------|-------------|-----------------------------|
| Autonomic symptoms       | 0·75 | points | improvement | $(0\cdot001 < P < 0\cdot1$  |
| Fears                    | 0·58 | "      | "           | $0\cdot02 < P < 0\cdot05$   |
| General somatic symptoms | 0·25 | "      | "           | $0\cdot02 < P < 0\cdot05$ ) |



The three symptoms previously mentioned continued to improve, but the amount was just below the accepted standard of statistical significance.

|              |      |                    |                     |
|--------------|------|--------------------|---------------------|
| Anxious mood | 0.42 | points improvement | $(0.05 < P < 0.10)$ |
| Tension      | 0.42 | „ „                | $0.05 < P < 0.10$   |
| Insomnia     | 0.42 | „ „                | $0.05 < P < 0.10$   |

No difference anywhere approaching statistical significance was found between the total improvement scores and sex or age of patients, or between the initial symptom score and improvement (either for the sexes together or separately).

At the original interview patients were graded into those with "marked", "slight", or "no" obsessional personality traits. It is of particular interest that there was no correlation between these gradings and improvement due to suggestion.

During the initial fortnight on inert tablets, the greatest amelioration occurred in those symptoms which most affect the patient subjectively (anxious mood, insomnia, tension) and it would appear that this accounts for the great subjective relief which is frequently noted after explanation and reassurance, not necessarily associated with the concomitant exhibition of inert tablets or medicines.

In the 12 patients who remained on dummy tablets for the full period of the trial, the initial improvement noted continued to a lesser degree during the last three weeks, but a marked beneficial effect was found in autonomic symptoms, fears and general somatic symptoms, and this effect is of high statistical significance. Thus it appears that as the placebo effect continues, the improvement of subjective psychic symptoms, marked at first, becomes less, and those anxiety symptoms mediated by autonomic and other somatic pathways improve considerably later.

### DISCUSSION

By making clinical assessments at two intervals in this enquiry, it has been possible to demonstrate that improvement was a continuous process over the five week observation period at least. Experimental investigations of "suggestion" have usually confined themselves to the more immediate effects, and in therapeutic trials, where a control group was given placebo, the processes occurring in the control group have largely been ignored. Attention has been paid to both these points in the present investigation. The use of a rating scale with specific items has shown that different symptoms respond to "suggestion" in different ways; in the first place they do not all start at the same time, and the rate of improvement is likewise variable. It is well known that patients exhibit different patterns or constellations of symptoms, but little attention appears to have been paid to the fact that even in the one patient these symptoms respond differently to treatment. As a matter of clinical experience, however, it is well recognized that patients may be left with "residual" symptoms at the end of treatment, or in other words, specific symptoms have shown this different response to therapeutic influences. We have been able to demonstrate this objectively and confirm it by the use of statistical tests.

Psycho-analysts have always emphasized the specificity of symptoms in relation to aetiology, *i.e.*, that particular experiences and mental mechanisms are related to particular symptoms. They have also emphasized that improvement of symptoms is related to the resolution of the appropriate unconscious

conflicts. The findings of the present investigation indicate that specific symptoms respond differently to "suggestion" also, although the limitations of the enquiry must not be overlooked. This is part of the ignorance on the results of psychotherapy in general, both long- and short-term. One may conclude that this enquiry underlines the need for adequate investigations, with suitable follow-up periods, on the results of various methods of psychotherapy (Whitehorn, 1948).

Although the term "suggestion" has been used here, it seems likely that the changes occurring in these patients must be ascribed to a "real" therapeutic effect. An experiment described by Glaser and Whittow (1954) showed that the suggestion effect produced by administering a drug lasted no more than three days, which is of a very different order from the 5 weeks we have found.

#### SUMMARY

1. A selected group of 34 patients suffering from anxiety states were assessed on a special rating scale before and after a period of two weeks, during which time inert tablets were prescribed and some measure of explanation and reassurance was employed. Twelve of these patients continued to receive inert tablets, etc., for a further three weeks.

2. Symptom scores after both periods show a statistically highly significant degree of improvement.

3. During the first period improvement was largely due to a diminution of the psychic manifestations of anxiety. During the second period the improvement continued, being mostly due to an amelioration of the somatic symptoms of anxiety.

#### ACKNOWLEDGMENTS

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# TREATMENT OF ANXIETY STATES

## II.—CLINICAL TRIAL OF BENACTYZINE IN ANXIETY STATES

By

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Of all the tranquillizers, it may well be said that benactyzine has had the most chequered history. After its synthesis, a series of most careful experiments on animals demonstrated its ability to reduce or modify behaviour induced by stress. The first clinical trial gave rise to high hopes of its value in treatment but as further trials, more carefully designed, were made the results became increasingly inconclusive.

Profound effects of benactyzine upon the central nervous system have been reported. These include the suppression of the normal rhythm of the EEG (Coady and Jewesbury, 1956), blocking of the effects of lysergic acid diethylamide (Glow, 1958), and diminution of the autonomic responses of human subjects to emotionally disturbing experiences (Jacobsen *et al.*, 1955). Subjectively, the effects of excess of benactyzine show themselves as a sort of "derealization", a general flattening of affect, some slowness of thinking and impairment of concentration. Our inability to derive conclusions from these experiments, relevant to the clinical field, is a measure of our theoretical insecurity and ignorance.

The following brief account of a clinical trial of benactyzine may be of interest not only as a test of the value of the drug, but also because it raises and illustrates certain problems of clinical trials.

There is little doubt that one of the great difficulties in conducting trials of tranquillizers is the presence of side effects, which can be equally troublesome in clinical use. Some "side effects", attributed to the action of the drug, in fact appear almost as often in patients receiving placebos (Scott Forbes and Earle, 1957). In view of this, when conducting a controlled clinical trial, it is not sufficient merely to use a group of patients given placebos in order to determine the value of the drug. The action of the drug will be concealed by side effects which occur equally among the patients treated with active drug and those treated with placebo. For this reason it is necessary to make assessments on the state of the patient not simply as an over-all change for better or for worse, but specifically and in detail. Only in this way can an adequate assessment be made of the effect of the drug, eliminating spurious symptoms. This is important, because in clinical practice such spurious side effects will tend to fade out in the course of time. Thus if the drug has any real positive effect one can afford to neglect its spurious side effects. Furthermore, a scale for assessing symptoms



will always be more reliable if the individual symptoms are rated separately. Such a scale is also of value in that it gives information on the specific nature of the improvement produced by treatment. This would be of particular importance if an enquiry were made comparing different treatments, e.g. different tranquillizers.

#### DESIGN OF THE TRIAL

It was decided to confine the trial to patients suffering from anxiety neurosis. Although depression is never entirely absent in anxiety states, particularly in chronic cases, all patients with marked depression were excluded. There are two reasons why the use of a homogeneous diagnostic group of patients is to be preferred in this sort of trial. The first is that it makes comparisons between one patient and another much easier. The second is that comparisons between patients in different diagnostic categories are difficult and the meaning of such comparisons is uncertain. The patients were all between the ages of 20 and 65 years and none had a history of more than 4 years illness. They were all treated as out-patients and seen weekly. At the first interview a full history was taken, the patients were given reassurance and explanation, and the illness discussed with them as appropriate to simple psychotherapy. For the first two weeks the patients also received a placebo tablet three times a day. This was done in an attempt to eliminate the effects of suggestion and initial reassurance before the trial itself started. At the end of two weeks a second psychiatrist was present at the interview and made an independent rating of the patient's symptoms. Patients were then put on the trial, which meant that they received either benactyzine or placebo tablets in accordance with a code which was known only to the hospital pharmacist. The patients were started off with three tablets a day and the dose increased to eight a day, unless they showed evidence of side symptoms, in which case the dose was reduced appropriately. After three weeks on the trial, they were again assessed by the same pair of physicians. None of the patients showed side effects at this interview. The assessments were made using a rating scale consisting of 13 variables, each rated on a five-point scale. The reliability of total scores for patients is very high (Hamilton, 1958).

At the end of the trial, all patients were taken off tablets, and then after a fortnight they were put on benactyzine. From the point of view of the patients, all were interviewed and given simple psychotherapy. Some were given benactyzine two weeks after the first interview, others not until seven weeks later.

It was observed, during the course of the trial, that a number of patients experienced markedly favourable or unfavourable changes in their circumstances which appeared to affect their symptoms. It was considered that this was equivalent to an additional treatment, and therefore these patients should not be included in the trial. (Such exclusion would not be necessary in a trial involving many patients, since these patients would tend to cancel out in the long run.) Before the code was broken, a conference was held between the three physicians at which each case was carefully revised in detail and it was decided whether it should be eliminated from the trial on the basis of the evidence available. Patients were eliminated when all three physicians were in agreement; there was no difficulty about this. The data for these patients is given in Table III. The following case history illustrates the problem:

A married woman of 38 years complained of headaches, dizzy attacks, palpitation, chest pains, dyspepsia, and "black outs" (mind goes blank). Symptoms began soon after she discovered that her third child was mentally defective (mongol). She was told he had to be treated very carefully to avoid chest illness. She devoted all her time to the child, who was allowed to have all his own way and eventually dominated the home. The child is over-active, and if thwarted creates havoc. During the last year the child has been described as an "unruly terror". The two older children have reacted to this by becoming increasingly difficult, contributing to the domestic chaos. The defective child was temporarily admitted to a mental deficiency hospital just before the patient came for treatment, but she was in a panic lest he return any moment.

While on the trial, permanent arrangements were made for the settlement of the child.

As many patients had shown side effects which might have been due to the drug, but not necessarily so, it is possible that the physicians suspected which patients had been given the drug and which the placebo. Such a suspicion might have biased them both in their assessment of the patient's condition and in the decision to discard them from the trial. It is possible to throw light on this by the fact that at the end of the trial, the patient was interviewed by two physicians, one of whom was ignorant of what the patient had undergone in the interval since the first double interview. The presence of bias could therefore be shown by comparing the scores given by the two physicians at the end of the trial. Table IV gives the essential information.

The physicians in charge of the patients have allotted a trivially larger score of improvement, than have their colleagues, to the patients given active tablets. The difference is statistically non-significant.

The scores of each patient at the beginning and end of the trial are to be seen in Table I. Two difficulties arise in the statistical analysis of the data. The first is that there is a fairly high correlation between the patient's improvement and the original score. This can be partly eliminated by measuring improvement as a percentage of the initial score (Hargreaves, Hamilton and Roberts, 1957) but this is not a satisfactory method. The second difficulty is that patients were assessed by three different pairs of physicians. The result could be influenced by bias of the pairs of physicians towards high or low scoring. Both of these difficulties can be eliminated by using analysis of covariance on a  $3 \times 2$  table (Table II).

### RESULTS OF THE TRIAL

If we consider the total score of a patient as a measure of his illness, and the change in score as a measure of his improvement, then the results show that although the patients who received the active drug improved more than the patients who received only placebo, this is statistically significant only at the 11 per cent. level. This means that such a result could have been obtained by chance alone, on the assumption that the drug has no effect, about 11 times in a hundred. This is below the usually accepted minimum standard of statistical significance.

It is of interest that the differences between pairs of physicians were quite trivial.

When we consider specific items of the scale, we find that the control group showed trivial worsening in Genito-Urinary and Respiratory symptoms. In the case of specific fears and depression, the control group showed some improvement and the treated group showed none. In all other symptoms, those in the treated group showed more improvement than those who had received placebo, but only in the case of "behaviour at interview" did the significance of the difference reach the 5 per cent. level. In five other categories of symptoms it lay between 10 per cent. and 20 per cent. (Table V).

Information was obtained from the patient on items which might be of prognostic significance. For example, if the patient has an anxious personality before the onset of his illness, does this affect the results of treatment? We found no relationship between the previous existence of an anxious personality and the amount of improvement, either with or without the drug. The same applies to "obsessional personality", the presence of precipitating factors, and a family history of mental illness. There is no relation between the length of history and the amount of improvement. All of these relations were quite insignificant statistically.

Although every attempt was made to include in the series only those patients who were suffering from an anxiety reaction without marked depressive features, it is a matter of great interest that some of them subsequently developed serious symptoms of depression and eventually had to be given E.C.T. All these patients made excellent recoveries.

TABLE I  
*Total Anxiety Scores of Patients at Start and End of Trial*

| Pairs of Physicians |    |    | I                |                | II               |                | III              |                |
|---------------------|----|----|------------------|----------------|------------------|----------------|------------------|----------------|
|                     |    |    | Initial<br>Score | Final<br>Score | Initial<br>Score | Final<br>Score | Initial<br>Score | Final<br>Score |
| Drug                | .. | .. | 61               | 49             | 42               | 28             | 31               | 20             |
|                     |    |    | 8                | 3              | 34               | 27             | 38               | 36             |
|                     |    |    | 23               | 12             | 28               | 7              | 41               | 34             |
|                     |    |    | 44               | 25             | 32               | 20             | 20               | 16             |
|                     |    |    | 14               | 4              |                  |                | 23               | 15             |
| Placebo             | .. | .. | 32               | 32             | 48               | 56             | 13               | 11             |
|                     |    |    | 39               | 25             | 27               | 15             | 31               | 34             |
|                     |    |    | 46               | 41             | 34               | 26             | 28               | 21             |
|                     |    |    |                  |                | 22               | 8              | 22               | 20             |
|                     |    |    |                  |                |                  |                | 87               | 22             |

TABLE II  
*Analysis of Covariance*

| Source                                 | d.f. | Sum of<br>Squares<br>Initial<br>Scores | Sum of<br>Cross-<br>products | Sum of<br>Squares<br>Final<br>Scores | Sum of<br>Squares<br>Initial<br>Scores | Sum of<br>Cross-<br>products | Sum of<br>Squares<br>Final<br>Scores | Source                               |
|----------------------------------------|------|----------------------------------------|------------------------------|--------------------------------------|----------------------------------------|------------------------------|--------------------------------------|--------------------------------------|
| Physicians .. (disregarding treatment) | 2    | 152.3                                  | 22.2                         | 4.2                                  | 153.8                                  | 31.8                         | 11.4                                 | Physicians (by subtraction)          |
| Interaction ..                         | 2    | 201.6                                  | 235.0                        | 299.6                                | 201.6                                  | 235.0                        | 299.6                                | Interaction                          |
| Treatments (by subtraction) ..         | 1    | 1.8                                    | 16.6                         | 154.4                                | 0.3                                    | 7.0                          | 147.3                                | Treatments (disregarding Physicians) |
| Between cells ..                       | 5    | 355.7                                  | 273.8                        | 458.3                                | 355.7                                  | 273.8                        | 458.3                                |                                      |
| Within cells ..                        | 20   | 3,198.8                                | 3,128.0                      | 3,893.6                              |                                        |                              |                                      |                                      |
| Total ..                               | 25   | 3,554.5                                | 3,401.8                      | 4,351.9                              |                                        |                              |                                      |                                      |
| Tests of Significance:                 |      |                                        |                              |                                      |                                        |                              |                                      |                                      |
| Regression                             | F    | 69.6                                   | P                            | < .001                               |                                        |                              |                                      |                                      |
| Interaction                            |      | < 1                                    |                              | —                                    |                                        |                              |                                      |                                      |
| Treatments                             |      | 2.81                                   |                              | .11                                  |                                        |                              |                                      |                                      |
| Physicians                             |      | 1.05                                   |                              | —                                    |                                        |                              |                                      |                                      |



TABLE III  
*Total Anxiety Scores of Patients Excluded from the Trial*

|                                  |    |    |    | Initial<br>Score | Final<br>Score |
|----------------------------------|----|----|----|------------------|----------------|
| Drug (circumstances worsened)    | .. | .. | .. | 29               | 31             |
|                                  |    |    |    | 15               | 5              |
|                                  |    |    |    | 54               | 26             |
| Placebo (circumstances improved) | .. | .. | .. | 24               | 22             |
|                                  |    |    |    | 30               | 12             |
|                                  |    |    |    | 14               | 7              |

TABLE IV  
*Comparison of Improvement Scores Allotted by Physicians*

|                                                               |    |    |    |    | Placebo<br>Group | Drug<br>Group |
|---------------------------------------------------------------|----|----|----|----|------------------|---------------|
| Number of patients                                            | .. | .. | .. | .. | 12               | 14            |
| Total improvement, scored by physicians in charge of patients |    |    |    |    | 34               | 73            |
| Total improvement, scored by extra physician                  | .. | .. | .. |    | 34               | 70            |

TABLE V  
*Improvement Scores in Specific Symptoms*

| Symptom                |    |    | Placebo<br>n=12<br>Total<br>Score | Drug<br>n=14<br>Total<br>Score | Total<br>Sum of<br>Squares | F Ratio | P<br>(%) |
|------------------------|----|----|-----------------------------------|--------------------------------|----------------------------|---------|----------|
| Anxious mood           | .. | .. | 13                                | 23                             | 112                        | —       |          |
| Tension                | .. | .. | 11                                | 16                             | 59                         | —       |          |
| Fears                  | .. | .. | 7                                 | 0                              | 23                         | 2.78    | 10-20    |
| Insomnia               | .. | .. | 9                                 | 12                             | 41                         | —       |          |
| Intellectual           | .. | .. | 2                                 | 13                             | 59                         | 1.91    | 10-20    |
| Depression             | .. | .. | 4                                 | 0                              | 31                         | —       |          |
| General somatic        | .. | .. | 7                                 | 8                              | 21                         | —       |          |
| Cardio-vascular        | .. | .. | 3                                 | 6                              | 51                         | —       |          |
| Respiratory            | .. | .. | -1                                | 7                              | 28                         | 2.13    | 10-20    |
| Gastro-intestinal      | .. | .. | 1                                 | 12                             | 71                         | 2.52    | 10-20    |
| Genito-urinary         | .. | .. | -3                                | 7                              | 44                         | 2.19    | 10-20    |
| Autonomic              | .. | .. | 14                                | 17                             | 95                         | —       |          |
| Behaviour at interview | .. |    | 1                                 | 13                             | 38                         | 4.26    | 5        |

#### SUMMARY

1. A clinical trial of benactyzine in anxiety states is described. All patients received simple psychotherapy, and in addition 14 received benactyzine and 12 were given blank tablets.

2. The patient's condition at the start and end of the trial was measured with a rating scale with items dealing with specific symptoms. Although greater improvement occurred in the patients given drug compared with those given placebo in 11 out of 13 items, in only one did it reach a level of statistical significance.

3. The use of two raters at the same interview provided evidence that knowledge of side effects did not influence ratings.

4. The amount of improvement is not related to the length of illness, the previous personality, the presence of precipitating factors or family history of mental illness.

5. The analysis of results was made complicated by a high correlation between original scores and amount of improvement, and by the use of three pairs of raters in the trial. This was dealt with by analysis of covariance.

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# TREATMENT OF ANXIETY STATES

## III. COMPONENTS OF ANXIETY AND THEIR RESPONSE TO BENACTYZINE

By

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THE assessment of the results of a treatment in any particular disorder is generally a very complicated one, by reason of the fact that the treatment does not usually improve all the manifestations of the disorder, and even when it does so, it does not affect them equally. The case of thyroid medication, which completely eliminates all the manifestations of thyroid deficiency, is an unusual one in medicine. Even where the pathological process may be completely stopped, as in general paresis and pulmonary tuberculosis, the patient may be left with residual loss of function due to irrevocable loss of normal tissue. In some cases the treatment itself may be of such a nature that the patient merely exchanges one disability for another. For example, the treatment of mild diabetes mellitus by a reducing diet may indeed eliminate the diabetes, but only at the cost of replacing it by chronic hunger and social restrictions, which many patients feel are worse than the original disease. In the end, they may give up their treatment. In some cases, the treatment has "complications", which means to the patient that he merely exchanges one set of symptoms for another. For example, he may exchange the symptoms of duodenal ulcer for those of dumping syndrome.

Psychiatrists are particularly aware of this problem, for in most cases, they are unable to comfort themselves over the deficiencies of their treatment with the thought that at least the pathological process has been stopped. A useful treatment is only too often one which merely ameliorates some of the symptoms from which the patient suffers. On occasions it exchanges less tolerable symptoms for more tolerable ones. It is for this reason therefore that the problem of the assessment of improvement in patients is more often discussed in psychiatry than in other specialities within medicine, rather than because it is fundamentally a more difficult problem.

The paper by Hargreaves, Hamilton and Roberts (1958), on the effects of benactyzine on anxiety neurosis can be considered from the point of view that it represents one particular method of dealing with this problem. In this investigation, 26 patients suffering from anxiety neurosis were randomly allotted into two groups, 14 receiving the drug and 12 receiving a placebo identical in appearance and taste. The patients were assessed before and after treatment on a special rating scale consisting of 13 items. The scores for the items were summed and the change in scores obtained by subtracting the second assessment from the first. The two sets of improvement scores were then subjected to statistical analysis, which demonstrated that although the treated group improved more than the control group, owing to the variability of the results from person to person, such a result could have been obtained by chance about 7 times in a hundred trials.



If one wishes to be really certain that the result is due to the "treatment" and not to chance, it is customary to reject any result which could have occurred by chance as often as once in a hundred trials. If one wants to be reasonably certain, it is customary to reject results which could have occurred by chance once in 20 trials. It is clear that this is an arbitrary decision. The investigator is involved in two alternative difficulties. If he adopts a stringent statistical test, he may reject a treatment that is giving a slight benefit. One example where this may be very important is where a series of compounds is being tried out for their therapeutic effect. If one compound gives a slight improvement, it may be possible to increase its effect by alterations to its composition. Too stringent a statistical test may mean that an important lead is not followed. On the other hand, if a low standard is accepted, it may be that a treatment is accepted when in fact it is valueless. Many patients will be submitted to this treatment before experience finally rejects it. The history of medicine contains so many examples of this that none need be specified.

There is a simple way out of the difficulty when a properly planned trial is made. Chance results, by definition, tend not to repeat themselves, and therefore, by increasing the number of cases investigated, the correctness of the decision to accept or reject the treatment can be made more and more certain. It is important to recognize that, while the conclusions about the results of a trial can be made more and more certain, the meaning depends entirely on whether the trial is considered from the practical or theoretical point of view. From the former point of view, when a new treatment is compared with an old one, it is of little account if it requires hundreds of cases to demonstrate that it is slightly superior. In fact, the final decision whether to accept it or reject it, will then depend on other considerations, such as the cost of the treatment (not only in money, but also in terms of time taken by physician or patient), the number and nature of side-effects, and the risks of complications. For example, the risks of "straight" E.C.T. are small but definite. So are the risks of administering an intravenous anaesthetic and a muscle relaxant. It is not yet at all certain which of these two is the greater. In the same way, the mortality which is to be expected from administering an anaesthetic to women in labour is comparable to maternal mortality as a whole. In both cases the advantages of the more "humane" method adds an imponderable factor which makes decision difficult, and leaves much room for individual judgment.

It may be added, in passing, that any substance which is able to interfere sufficiently with normal vital processes to be of value in therapeutics, is bound to be capable of giving rise to deleterious "side-effects". Eventually, in any disease, a point will be reached where the advantage of a new drug may be counter-balanced by its disadvantages. When that point is reached, the medical profession will have to change its traditional attitude. Heretofore, when a new treatment was proclaimed to be more effective than an old one, it was the moral obligation of the practitioner to give his patients the benefit of it. The medical profession is now reaching the stage when it is beginning to demand evidence that the new treatment is effective. Hence the increasing emphasis on the need for properly planned trials. Eventually, the demand will be that the new treatment be not only better than the old, but be proved not to have disadvantages that outweigh its benefits, and it will be considered wrong to subject patients to the new treatment until this point has been *proved*.

On the other hand, from the theoretical point of view, when a new treatment shows only a very slight advantage over the old, it may yet give a lead for further research. There is one exception to these general principles, and that is where a

new treatment produces a very slight improvement in mortality, for in this case, it may mean the difference between life or death to an individual patient. Nevertheless, even here the dangers from side-effects and complications may have to be considered.

These considerations make it worth while to examine the results of the benactyzine trial in detail. It will be shown that conclusions can be drawn from it that are of great theoretical significance, and which should serve as the starting point for further research that may be of great practical value.

The first point to consider is the method of assessment of the patient's condition and improvement. This was done by rating each symptom on a five-point scale, ranging from absent (given a score of 0), through mild or trivial (scored 1), moderate (scored 2), severe (scored 3), to very severe (scored 4). It is clear that this is a very arbitrary arrangement. In the first place, each symptom is given equal weight in summing to obtain a total. While there could be much disagreement on how much greater weight should be assigned to one symptom compared with another, everybody would agree that there is no justification for giving an equal weight to all the symptoms, other than that it has the merit of simplicity and convenience for the statistician; and that means, no merit at all clinically.

Another aspect of this arbitrary scoring system, that is even less justifiable, is that the same weight is given to a change from any one category to the adjacent one. The disappearance of a mild or trivial symptom is given one point of improvement, and this is equal to the change from a moderate grade to a mild one, and from a severe to a moderate one, and so on. Leaving aside the question of how any such decision is to be made, there is no evidence that such an unlikely equality is justified.

Another point that is not obvious without a detailed examination of the data, arises from the fact that some variables have high correlations with a few others, and almost zero correlations with yet others. A change in one of the highly correlated variables will tend to be accompanied by changes in the others, and therefore the patient will tend to accumulate a large number of points of improvement. On the other hand, improvement in a variable which has low correlations with others, will show itself only in that one, and the patient will show a low improvement score. Against this it may be argued that this is true, in general, for all the patients, particularly so since they form a fairly homogeneous group, all suffering from anxiety neurosis, all out-patients. This may be so, but individual differences do exist, and they may be important. This problem will be considered later.

The most important difficulty lies in the fact that the scores on the 13 variables are summed to give a total score, which is supposed to give an overall assessment of the severity of the patient's condition, regardless of how the total score is arrived at, i.e. from what symptoms it is derived. The justification for this procedure is that it is intuitively felt to be a reasonable approximation to the judgment that is made when one patient is considered to be more or less ill than another. Nevertheless, there are many critics of what is not unreasonably regarded as an "atomistic" procedure, and these critics prefer to come to an overall assessment without the help (or hindrance) of such a mechanical method. The answer to this criticism is that experience, supplemented by innumerable experiments, has shown that the method of overall assessment is extremely unreliable, i.e. it cannot be reproduced by another physician, or even by the same physician on two different occasions; whereas the mechanical method is highly reliable. And this has been demonstrated in this particular trial.

The point can be put in another way. By substituting a summed score for the individual 13 scores, we are trying to use a single number to represent the 13 numbers. Such a number is known as an "index number", and the information we obtain from it is supposed to epitomize the information available in its constituents. "Epitomize" is a good word to cover the fact that information is lost in the process, and this loss may be considerable. The "cost of living" is an example of an index number which experience has shown is singularly deficient in information. More information can be retained by constructing two, three and more index numbers. The limit of the process is reached when we have thirteen index numbers, i.e. when we retain all the original variables. The difficulty here is that it is almost impossible to grasp, and to detect any significance, in the simultaneous changes of many variables. The problem is then to decide how many index numbers are required to give adequate information, subject to the opposing limitations, that the fewer numbers, the less information, whereas the more, the greater difficulty to grasp.

A technique exists for handling this problem; the technique of "factor analysis". A full understanding of the underlying theory requires a certain amount of mathematical sophistication, but the principles can be easily understood by the non-mathematical through the following approach.

In so far as two variables are correlated, this correlation may be ascribed to an element common to them. Each variable may be considered as consisting of an element common to both and a specific element which is unrelated. When a group of variables are all positively correlated, they each may be regarded as containing (or measuring) an element common to them all, and a specific element. This common element (usually called a general factor) may be regarded as a sum or average of all the variables, for their sum or average summates what is common to them, whereas the specific elements tend to be cancelled out. This is not entirely so, since after the general factor is removed from the variables it is usually found that the variables fall into groups which show, by their positive correlations, that a common element may still be regarded as existing within the groups; this is called a group factor. When this too is removed, a further common element may be found amongst smaller groups, and so on, until negligible correlations, "residuals", are all that is left.

Returning to the previous metaphor, each of these factors may be regarded as an index number, and the method of obtaining them demonstrates the minimum number of such indices which will effectively contain all the information to be found in the separate variables. Factors have another advantage, and that is that by suitable methods it is possible to obtain them in such a way that they are uncorrelated. This immediately eliminates the difficulties in scoring arising from the correlations between variables.

Since the factors are obtained via the correlations, this involves a change in the method of weighting the individual variables. The standard deviations of the variables are first made equal, and the calculations proceed with these "standardized" scores. There is still an arbitrary quality in the weighting system, but it is related to the standard deviation of each variable, and this is a property of the group of patients, and therefore of the population of patients of which the group may be regarded as a sample.

Finally, the problem of assigning a suitable weight to a change from one grade to another, could be dealt with by "normalizing" the scores, i.e. ensuring that they form a normal distribution. It is true that this is still somewhat of an artificial arrangement, but it does relate the individual score to the population of patients, and has the merit that it makes prediction more accurate (when this



is required) and makes tests of significance more reliable (since they are based on normal distributions). In practice, unless the range of scores is large, the difference produced by normalization is usually very small.

To return to the present investigation. The thirteen variables were inter-correlated, and three factors extracted from the resulting matrix of correlations. Using a simplified approximate method, formulae were obtained for calculating the factor measurement for each individual patient. This method has the slight disadvantage that the factor measurements so obtained are not completely uncorrelated, but Table I shows that the correlations are in fact quite low. Furthermore the standard deviations, which should all be approximately ten,

TABLE I  
*Correlations, Means and Standard Deviations of Factor Measurements*

|                    |    |    |    |    | General Factor | First Bipolar | Second Bipolar |
|--------------------|----|----|----|----|----------------|---------------|----------------|
| E                  | .. | .. | .. | .. | 1.00           | .17           | -.33           |
| BP <sub>1</sub>    | .. | .. | .. | .. | .17            | 1.00          | .19            |
| BP <sub>2</sub>    | .. | .. | .. | .. | -.33           | .19           | 1.00           |
| Mean               | .. | .. | .. | .. | 50             | 50            | 50             |
| Standard deviation | .. | .. | .. | .. | 10.4           | 7.3           | 5.1            |

diminish with each succeeding factor. For each factor, the mean of the measurements is 50, and this shows clearly the artificial nature of these measurements. It must be emphasized that what is artificial is the actual number allotted. For example, it could have been arranged that the mean was 100 and the standard deviation 15, as is customary in intelligence tests. The use of the term "index number" for a factor measurement, is made obvious by these figures.

The factor measurements were calculated for each patient at the beginning of the clinical trial and at the end. The amount of improvement was obtained by subtracting the latter figure from the former. We are now in a position to determine whether the patients treated with benactyzine show any significantly greater improvement than those given placebo. This is done by comparing the mean improvement of the two groups by means of the *t* test. The results are in Table II.

TABLE II  
*Tests of Significance of Improvement*

|                                      |    | G     | BP <sub>1</sub> | BP <sub>2</sub> |                    |
|--------------------------------------|----|-------|-----------------|-----------------|--------------------|
| Total improvement for 12 patients    | .. | 52    | 44              | 30              | Control series     |
| Sum of squares of improvement scores |    | 702   | 392             | 408             |                    |
| Total improvement for 14 patients    | .. | 124   | 55              | -46*            | Benactyzine series |
| Sum of squares of improvement scores |    | 1,314 | 803             | 348             |                    |
| <i>t</i>                             | .. | 2.14  | below 1         | 3.13            |                    |
| <i>p</i>                             | .. | .05   | N.S.            | below .005      |                    |

\* The allocation of signs in bipolar factors is arbitrary. The results have the same meaning for a total improvement score of -30 for controls, and +46 for treated.

For the first (general factor) the test shows a probability of 5 per cent. This is the same as that obtained with the original simple sum of crude scores. The result confirms the statement that the general factor may be regarded as a sum of the separate variables. It would not be an unjustifiable criticism to point out that in this case, a very long and laborious route has been taken to achieve something which could just as easily have been done by the simplest and crudest

of methods. At best, it can be said that a refined technique has defended a crude method against obvious criticism.

The second factor shows negligible difference between the two groups, but the third factor shows a highly significant difference between the treated patients and controls. On the overall assessment of anxiety, benactyzine has had some slight benefit, but there can be no doubt about its effect on the particular combination of symptoms which is represented by the third factor.

The third factor accounts for only 7 per cent. of the total variance, i.e. it plays only a small part in the total variability measured by the 13 variables. It is not surprising therefore, that a significant improvement in this factor makes very little difference to the patient's state. Although benactyzine makes a considerable improvement in that combination of symptoms represented by the third factor, it is of no great value in the treatment of anxiety neurosis as such. For those patients whose symptoms are predominantly those which form the third factor, it would probably be of great help.

The nature of the factors can be inferred by considering the factor saturations, i.e. the correlations between the variables and the factor, or the weights given to the standardized scores in computing the factor measurements. The first factor is a general factor of anxiety, and sums all the variables. The second contrasts somatic with psychic symptoms. The third runs as follows (the first figure gives the saturation and the second the weight, both multiplied by a hundred):

General Somatic (47, 29), Fears (42, 22), Insomnia (28, 27), Autonomic (25, 9), Tension (7, -2), Cardiovascular (5, -1), Anxious Mood (2, -5), Gastro-intestinal (-8, -6), Respiratory (-15, -13), Cognitive (-15, -13), Behaviour (-32, -18), Depression (-32, -27), Genito-urinary (-34, -25).

The question naturally arises: Do such patients constitute a special group, distinguishable from other patients diagnosed as suffering from anxiety neurosis? Can they be distinguished on other grounds? No legitimate conclusions can be drawn by further examination of this group of patients, but the questions raised are of sufficient importance to justify further investigation.

Progress in medicine often depends on the discovery of new tools for investigation. One of these is what may be described as the therapeutic test. For example, there is an important difference between those macrocytic anaemias that respond to cyanocobalamin and those that do not. Whatever one may think about the distinction between endogenous and reactive depression, or between psychotic and neurotic depression, there is no doubt about the importance of the difference between those depressions that respond to E.C.T. and those that do not. When we understand the nature of this difference, we shall know something important about depressive states. It may be that this small trial of benactyzine will give us a clue about anxiety states.

#### SUMMARY

A controlled trial of the drug benactyzine was carried out on 26 patients suffering from Anxiety Neurosis, using a rating scale for 13 symptoms (variables). The relations between the variables show that they may be effectively replaced by three independent index numbers or factors. Replacing the thirteen measures for each patient by three factor measurements, the improvement occurring in each patient was then calculated. On comparing the mean improvement produced by benactyzine and that occurring in the controls, statistical tests show that this difference is highly significant in the case of the third factor. The implications of this are discussed.

## ACKNOWLEDGMENTS

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# ELECTROPLEXY (E.C.T.) TECHNIQUES IN CURRENT USE

## A REPORT OF A QUESTIONNAIRE RECENTLY CIRCULATED TO HOSPITALS

By

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### INTRODUCTION

AT a recent court case (40), the plaintiff, who sustained bilateral acetabular fractures following unmodified electroplexy, maintained that the defendants were guilty of negligence by failing to use relaxant drugs to prevent the risks of injury.

A number of experienced medical witnesses failed to agree upon a uniform technique of electroplexy. Some favoured the routine use of muscle relaxants, whereas others did not, and this resulted in the verdict being returned in favour of the defendants, and also brought the various problems associated with the administration of electroplexy very much before the public eye.

Summing up, the Judge stated that "a professional man was not guilty of negligence if he acted in accordance with a practice which was accepted by a competent body of men skilled in that particular art, merely because there was a body of opinion which took the opposite view". He emphasized that the use of E.C.T. was progressive, and that "the jury must not look with 1957 spectacles at what happened in 1954", suggesting that failure to use relaxants might now be considered negligent.

### A SHORT SURVEY OF THE LITERATURE

Previous writers show much disagreement about the best techniques of giving E.C.T., especially since the introduction of the short-acting relaxant drugs, and the routine use of unmodified E.C.T. still has a number of advocates. Kalinowsky (17), writing before the short-acting relaxants were in common use, commented that straight E.C.T. was a surprisingly harmless procedure, and that any recommendations complicating its simplicity should be carefully tested as to their safety. Tyndel (37) maintained that there was no justification for the use of muscle relaxants with or without anaesthesia, and Sargent and Slater (34) asserted that "to add Pentothal and a relaxant to E.C.T. is to add two potential sources of danger, each carrying its own risks of death". This view was shared by Maclay (24), and Eyres (6), and Impastato (16) considered that many fatalities attributed to E.C.T. resulted from pre-medication with relaxants, and quoted five patients who died after receiving relaxants prior to E.C.T.

The opposite view was taken by Bennett (2) who maintained that any form of straight convulsive shock was contraindicated, and more recently by Kelleher

and Whiteley (19) and Murphy (28) who felt that there could be little justification for electroplexy without muscle relaxants.

Opinions differed as to whether muscle relaxants should be administered in conjunction with an intravenous anaesthetic or alone, and in the choice of relaxants. *Monro et al.* (27), Fisher and Bannister (8) and Esplen (5) considered that it was essential to administer a quick-acting barbiturate either before or with the relaxant, because of painful muscular fasciculation and respiratory distress associated with the intravenous injection of these substances alone. Stevens and Tovell (36) favoured Pentothal in addition to suxamethonium chloride ("Scoline") to eliminate anxiety during drug induced relaxation, and Lincoln and Broggi (21) alleged that the use of an anaesthetic tended to reduce the occurrence of post-treatment excitement.

Little and Reid (22) found buthalitone sodium ("Transithal") a superior anaesthetic to Pentothal, in that it appeared to antagonize the delayed return of breathing brought about by Scoline, though it does not appear that this anaesthetic is in current use in association with electroplexy.

The use of relaxants without anaesthesia was first tried out by Gillie and McNeil (9), and Kelleher and Whiteley (19) favoured E.C.T. modified with either Scoline or suxethonium bromide ("Brevedil E") alone, because it was safer, less time consuming and less complex than when given with Thiopentone. Fisher (7), advocating the use of Brevedil E alone, asserted that there was an added risk to life when Thiopentone was used. Beresford Davies (3) shared this view, and considered that Thiopentone increased the danger of laryngeal spasm, particularly if given in small doses.

Kelleher and Whiteley (19) and *Monro et al.* (27), after careful clinical comparison, preferred Scoline as a relaxant to Brevedil E, and *Monro* stated that he would have been completely satisfied with Scoline were it not for reported cases of prolonged apnoea after the use of this preparation, in association with E.C.T. (14), and in other cases (11, 12, 23).

Grant (10) described a case of respiratory paralysis lasting 2-3 post-operative days after a dose of 80 mg. of Scoline. *Impastato* (15) summarized the causes and treatment of apnoea following Scoline modified E.C.T., and described the use of a test-dose of 5 mg. of Scoline to determine the sensitivity of the respiratory centre to this preparation.

Prolonged apnoea does not appear to have been reported after Brevedil E, which *Wolfers* (38) and *Gillie* and *McNeil* (9) found to be an extremely satisfactory relaxant for modifying electrically induced convulsions both with and without anaesthesia. *Malone* and *Blayney* (25) commented on the extreme shortness of action of Brevedil E, and that its effect might have worn off if for any reason a second electrical stimulus had to be applied. *Fisher* and *Bannister* (8) and *Malone* and *Blayney* (25) reported that the shorter period of apnoea resulting from an injection of suxethonium bromide ("Brevedil E") gave the compound a decided preference over suxamethonium bromide ("Brevedil M") though *Danik* (4) regarded the latter preparation as an ideal muscular relaxant for use with E.C.T.

A few writers favoured the electrical modification of electroplexy and used the *Ectonus* method of E.C.T. administration, an improved version of the old "Glissando" technique. The principles of this method have been described by *Russell* (31 and 32) who claimed that muscle relaxants could be safely discontinued when the *Ectonus* technique was employed, which also relieved patients of anxiety associated with premedication and injections (33). However, in a later communication, these workers stated that "there will always be a few

special cases in which the additional precaution of a muscle relaxant is judged essential", and devised a modifying technique combining the smoothing effect of Ectonus E.C.T. with the partial effect of a muscle relaxant.

Kelleher and Whiteley (20) described the occurrence of cyanosis following the use of Ectonus E.C.T., possibly resulting from the Valsalva phenomenon, but this was subsequently denied by Russell and his co-workers, and has not been the experience of this author.

There have been a number of conflicting statements concerning the therapeutic effectiveness of unmodified versus modified electroplexy. Mayer-Gross, Slater and Roth (26), Fisher and Bannister (8) and Lincoln and Broggi (21), considered that the psychiatric results from modified E.C.T. were at least as good as those from unmodified E.C.T. Ardis and Wyllie (1) also shared this view, but noted that in a few instances this was apparently not the case. Later Fisher (7) alleged that the results of E.C.T. were more effective and long-lasting if there was no previous anaesthesia, and Seager (35), after a series of carefully controlled observations, confirmed the previous clinical impressions of his staff, that patients treated by unmodified E.C.T. were in hospital for a shorter period, received less treatments, and were more likely to remain well than those treated by modified E.C.T. However, Holmberg *et al.* (13) found that modified E.C.T. was of greater benefit in the treatment of endogenous depressions than unmodified E.C.T., because of the prolongation of convulsions brought about by modification, though the results were not statistically significant.

#### THE QUESTIONNAIRE

It is difficult to conceive of another effective treatment used in medicine to an extent comparable with electroplexy about which so many differences of opinion relating to administrative technique appear to exist. These differences are well illustrated in the contradictory replies of the professional witnesses at the recent court case, and are reflected in the opinions of numerous writers on the subject. In view of this, it was considered important to ascertain which techniques of electroplexy were in current practice at various teaching centres and mental hospitals in this country.

The questionnaire seemed the most appropriate method of obtaining this information. At the same time it was regarded as an excellent opportunity to collect some further data about electroplexy, which might not only be of general interest, but would undoubtedly be of particular value in helping to clarify some of these controversial issues, should any further cases of litigation arise.

Fifty-five copies were circulated to thirteen teaching hospitals in London and to forty-two mental hospitals on 20 June, 1957. The mental hospitals represented those where it was known that E.C.T. was carried out on large numbers of patients.

The questionnaire was addressed to the Physician Superintendents of mental hospitals and to the Consultants in charge of the Psychiatric Departments of teaching hospitals, who were asked to state:

1. The technique of electroplexy in current practice in their hospital on *male* patients. Males were selected because their convulsions following unmodified E.C.T. were more powerful than in females, and hence more liable to result in skeletal complications (18). A list of techniques followed, and they were requested to mark one only with a cross.

(a) E.C.T. unmodified . . . . .

(b) E.C.T. modified by Ectonus . . . . .

(c) E.C.T. modified by Brevedil E alone . . . . .



- (d) E.C.T. modified by Scoline alone .....
  - (e) E.C.T. modified by Pentothal and Brevedil E .....
  - (f) E.C.T. modified by Pentothal and Scoline .....
  - (g) E.C.T. modified by Pentothal alone .....
  - (h) E.C.T. modified by other anaesthetic and/or relaxant. Indicate which ....
  - (i) E.C.T. by any other technique and reasons for use .....
2. Any particular techniques of performing electroplexy that were disfavoured and why .....
  3. Whether E.C.T. was given by single or repeated multiple shocks .....
  4. Whether E.C.T. was given by a single shock or modified by Ectonus when relaxants were used .....
  5. Whether the services of a Consultant Anaesthetist were employed when anaesthetics and relaxants were administered .....
  6. The number of treatments given to new admissions in cases of:
    - (a) Schizophrenia .....
    - (b) Depression .....

### RESULTS

By the early part of August, 1957, some 47 (85 per cent.) completed copies of the questionnaire had been returned, which was regarded as an excellent response, and taken to indicate a wide interest in the subject. Twelve (92 per cent.) out of thirteen teaching hospitals, and thirty-six (86 per cent.) out of forty-two mental hospitals satisfactorily completed the proforma. Current practices at this hospital in respect of all six items were added to information obtained from the completed questionnaires, and incorporated in the results.

Replies to item 1 are listed in Table I. It appears that E.C.T. modified by Pentothal and Scoline was by far the most popular technique in current practice, being used at some 60 per cent. of hospitals. At some 85 per cent. of the hospitals contacted, E.C.T. was given with relaxants.

TABLE I  
*E.C.T. Techniques in Current Use*

| Technique                                               | No. | Per cent.<br>of Replies |
|---------------------------------------------------------|-----|-------------------------|
| (a) E.C.T. unmodified .. .. .                           | 1   | 2                       |
| (b) E.C.T. modified by Ectonus .. .. .                  | 3   | 6                       |
| (c) E.C.T. modified by Brevedil alone .. .. .           | 4   | 8                       |
| (d) E.C.T. modified by Scoline alone .. .. .            | 1   | 2                       |
| (e) E.C.T. modified by Pentothal and Brevedil E .. .. . | 7   | 15                      |
| (f) E.C.T. modified by Pentothal and Scoline .. .. .    | 29  | 60                      |

At a number of hospitals more than one technique were used, but the figures in the table refer to those techniques that were practised solely or in the vast majority of cases, and hence the percentage column does not quite total one hundred.

At a few hospitals other methods of modification were practised such as Evipan with Brevedil M, and Leptazol with Brevedil E, and at one Flaxedil was used.

At eleven (92 per cent.) out of twelve teaching hospitals electroplexy was modified with Pentothal and Scoline. At the remaining hospital, whilst it was customary to use the Ectonus technique for the vast majority of cases, Ectonus E.C.T. with Pentothal and Brevedil E was occasionally given to frail patients.

At one teaching hospital unmodified E.C.T. was only used in conjunction with insulin, and there they considered dangerous the combination of anaesthetic, relaxant and insulin.

At eighteen (50 per cent.) of the mental hospitals that completed the proforma electroplexy was modified with Pentothal and Scoline. At one mental hospital it was reported that some patients actually preferred unmodified E.C.T., though at another they were said to dislike it. At another unmodified electroplexy was only used when there appeared to be no response to modified treatment.

Replies to item 2 were illuminating, and tended to indicate that in many hospitals the technique of administration of E.C.T. often appeared to depend upon a process of elimination of other techniques, rather than upon any special merits of the method itself. The numbers of replies in which the separate techniques were disfavoured are shown in Table II.

TABLE II  
*Techniques Disfavoured*

| Technique                                               | No. |
|---------------------------------------------------------|-----|
| (a) E.C.T. unmodified .. .. .                           | 20  |
| (b) E.C.T. modified by Ectonus .. .. .                  | 4   |
| (c) E.C.T. modified by Brevedil E alone .. .. .         | 7   |
| (d) E.C.T. modified by Scoline alone .. .. .            | 9   |
| (e) E.C.T. modified by Pentothal and Brevedil E .. .. . | 3   |
| (f) E.C.T. modified by Pentothal and Scoline .. .. .    | 4   |
| (g) E.C.T. with Pentothal alone .. .. .                 | 3   |

Techniques that were in current practice at some hospitals were actively disfavoured at others. As might have been expected, dislike of a particular method often followed a single incident, e.g. a case of "Scoline terror", and it was evident that the choice of technique appeared to depend to a large extent on the personal bias of the doctor concerned. A substantial body of opinion was against the use of unmodified E.C.T. mainly because of skeletal complications, and was against the use of muscle relaxants without anaesthesia on humanitarian grounds, because of unpleasant subjective effects, not always entirely eradicated by the amnesia resulting from the treatment itself.

At four mental hospitals there was definite opposition to the modification of E.C.T. by Pentothal and Scoline. At one of these it was not considered justifiable to use Pentothal with relaxants as a routine, because of prolonged apnoea and experienced fatalities following the use of Scoline in a few instances. At this hospital the process of changing over syringes containing an anaesthetic to one containing a relaxant during the performance of the technique was criticized, and it was also asserted that pentothal alone did not modify the convulsion, and was safer when used with a relaxant than by itself.

At another hospital it was alleged that Scoline was too long-acting to be used in conjunction with electroplexy, whereas Brevedil E, because of the extreme shortness of its action, in some instances failed to modify the convulsion. The replies to this item of the questionnaire also contained numerous references to headaches following the administration of Pentothal.

A number of doctors stated that they had not yet tried the Ectonus technique, while at one hospital this method had been abandoned because of repeated failure of the Ectonus machine.

Replies to items 3 and 4 showed that it was customary at the majority of hospitals to induce E.C.T. by means of a single shock, though at one hospital

multiple shocks, and at four both techniques were practised. When relaxants were given, the majority favoured E.C.T. by a single shock, but at a few hospitals the Ectonus technique was also used. These results are summarized in Tables III and IV.

TABLE III  
*The Use of Single or Multiple Shocks*

|                 | Method |    |    |    |    |    |    |    |    | No. |
|-----------------|--------|----|----|----|----|----|----|----|----|-----|
| 1. Single       | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 38  |
| 2. Multiple     | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 1   |
| 3. Both 1 and 2 | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 4   |
| 4. Ectonus      | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 2   |

TABLE IV  
*Electrical Technique Used with Relaxants*

|                 | Method |    |    |    |    |    |    |    |    | No. |
|-----------------|--------|----|----|----|----|----|----|----|----|-----|
| 1. Single shock | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 32  |
| 2. Ectonus      | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 5   |
| 3. Both 1 and 2 | ..     | .. | .. | .. | .. | .. | .. | .. | .. | 3   |

Replies to item 5 indicated a sharp difference of opinion concerning the advisability of having a consultant anaesthetist in attendance when electroplexy was modified with anaesthetics and relaxants, and are shown in Tables V and VI. Where mental hospitals were concerned, opinions were fairly evenly distributed (Table V), but at most teaching hospitals the presence of an anaesthetist (of various grades) during the performance of electroplexy was the rule (Table VI). At three mental hospitals "Anaesthetist Coverage" alone

TABLE V  
*Anaesthetists at Mental Hospitals*

| Existing Arrangements                          |    |    |    |    |    |    |    |    | No. |
|------------------------------------------------|----|----|----|----|----|----|----|----|-----|
| No anaesthetist                                | .. | .. | .. | .. | .. | .. | .. | .. | 14  |
| Consultant anaesthetist                        | .. | .. | .. | .. | .. | .. | .. | .. | 10  |
| General practitioner or registrar anaesthetist | .. | .. | .. | .. | .. | .. | .. | .. | 4   |
| Occasional anaesthetist                        | .. | .. | .. | .. | .. | .. | .. | .. | 4   |

TABLE VI  
*Anaesthetists at Teaching Hospitals*

| Existing Arrangements                     |    |    |    |    |    |    |    |    | No. |
|-------------------------------------------|----|----|----|----|----|----|----|----|-----|
| No anaesthetist                           | .. | .. | .. | .. | .. | .. | .. | .. | 3   |
| Consultant anaesthetist                   | .. | .. | .. | .. | .. | .. | .. | .. | 4   |
| Consultant or registrar anaesthetist      | .. | .. | .. | .. | .. | .. | .. | .. | 2   |
| Registrar or house physician anaesthetist | .. | .. | .. | .. | .. | .. | .. | .. | 3   |

was considered sufficient, without the necessity of a consultant anaesthetist actually being in attendance.

At four teaching hospitals, consultant anaesthetists were always present when E.C.T. was being given, but at three the anaesthetists were in the Registrar or House Officer grade. At two, either consultants or registrars were employed depending upon availability, and at three no anaesthetist was present.

Two of the teaching hospitals appeared to depart from their routine practices where private patients were concerned. At one, the consultant



psychiatrist always gave the anaesthetic himself, while at the other a consultant anaesthetist was always in attendance.

There was a wide variation in the replies to item 6. Whilst at some hospitals no fixed courses of treatments were given, at others electroplexy ranged from one to over twenty individual treatments for schizophrenia, and from one to sixteen for depressions. The average numbers for the two conditions were calculated, and are shown in Table VII. At a few hospitals it was maintained that E.C.T. was not the treatment for schizophrenia, and that the type of depression was important when determining the number of treatments to be given.

TABLE VII  
*The Average Number of Treatments in Schizophrenia and Depression*

|               | Diagnosis |    |    |    |    |    |    |    | Average Number of Treatments |
|---------------|-----------|----|----|----|----|----|----|----|------------------------------|
| Schizophrenia | ..        | .. | .. | .. | .. | .. | .. | .. | 9                            |
| Depression    | ..        | .. | .. | .. | .. | .. | .. | .. | 6.5                          |

DISCUSSION

It is shown in Table I that at some 60 per cent. of the hospitals that responded to the questionnaire, modified E.C.T. with Pentothal and Scoline is the current practice. If, therefore, the contentions raised by Fisher (7) and Seager (35) are correct, that the results from modified E.C.T. are less satisfactory than those from unmodified E.C.T., then these hospitals, which represent a substantial majority, may be depriving their patients from the maximum therapeutic benefits of electroplexy. A hint that this state of affairs existed was made at one mental hospital, where modified E.C.T. was the routine, for it was there alleged that unmodified E.C.T. was "often found efficacious following no response to modified treatment".

It also would appear from this table that when Pentothal is given, Scoline is used more frequently than Brevedil E, possibly because Brevedil E and solutions of thiopentone are incompatible (38), though they may be given in separate syringes. Without anaesthesia, Brevedil E is used more commonly than Scoline.

A marked difference exists between the number of teaching hospitals that use the pentothal and scoline technique, compared with the number of mental hospitals (92 per cent. against 50 per cent.), and is undoubtedly related to the different staff-patient ratios at the two types of hospital. Compared with a mental hospital, the numbers of persons undergoing electroplexy at a teaching hospital are likely to be relatively small, and anaesthetists are more readily available. Also at many mental hospitals where large numbers of electrical treatments may have to be carried out, the Pentothal and Scoline technique, being the most time-consuming, is often the least practical, and recourse must be had to other methods.

The replies to item 2 indicated the important role played by the doctor's personal bias in determining the choice of technique to be followed, and the case of "Scoline terror" is a good example of this. Kalinowsky and Hoch (18) refer to a fear of E.C.T. which may develop after a certain number of treatments, and it may well be impossible to distinguish this from that which may accompany the intravenous injection of a short-acting muscular relaxant. To condemn a technique on such uncertain evidence is hardly justifiable, when the alternative, which involves the additional use of an anaesthetic, may turn out to be a more

dangerous procedure. This latter view appeared to be shared at a number of hospitals where relaxants without anaesthesia were employed as a routine, and it was found to be an extremely satisfactory method of modifying E.C.T., that hardly ever gave rise to any unpleasant subjective effects. A great deal seemed to depend on the time interval between the injection and the application of the stimulus, for if this was too long there was more chance of unpleasant choking sensations being remembered. In this respect Brevedil E, being quicker-acting, was superior to Scoline, and certainly safer as judged by reports in the literature. Headaches following the use of both relaxants have been observed by Wolfers (38), but Pentothal may also be responsible for this as suggested from the replies to the questionnaire.

Opinions varied less concerning the electrical modification of E.C.T. than they did with regard to the other items asked, for in most cases electroplexy was given by means of a single shock. However, at one teaching hospital two shocks were sometimes given during the first 3-4 treatments in agitated cases, which was a practice advocated by Kalinowsky (17) and Reitman and Delgado (30), the latter authors employing two or sometimes three sub-threshold stimuli to delay and soften the onset of the seizure, with Pentothal and Scoline pre-medication. These views are in sharp contrast to the opinion expressed at one teaching hospital, that the use of any apparatus which allowed the passage of current for more than 0.1 second gave rise to brain damage, which would preclude not only multiple shocks and repeated sub-threshold stimuli, but also the Ectonus technique.

There was a sharp difference of opinion concerning the necessity of having an anaesthetist in attendance when electroplexy was modified. At half the mental hospitals from which replies were received, anaesthetists were available on treatment mornings, but at the remainder anaesthetics and relaxants appeared to be given by the psychiatric registrar, sometimes single-handed, who may or may not be familiar with anaesthetic techniques, and with methods for coping with emergencies. It is difficult to find justification for this arrangement, when it has been clearly stated (39) that "only in exceptional circumstances should an operator acting alone also function as an anaesthetist". When this view is accepted, and bearing in mind the present shortage of anaesthetists to carry out this type of work in mental hospitals, there is a strong argument in favour of abandoning techniques involving the use of thiopentone, for as was stressed by Kelleher and Whiteley (20), insistence upon the presence of an anaesthetist on all occasions "might impose an impossible condition on the administration of E.C.T.". Other writers, such as Lincoln and Broggi (21) always have an anaesthetist in attendance during the performance of electroplexy, but the opposite view was taken by Seager (35), who did not consider that an anaesthetist was necessary provided that the psychiatrist had knowledge of the principles involved in dealing with an unconscious patient, given by Mushin (29), and stated that this applied equally to both unmodified and modified E.C.T.

Regarding the numbers of individual treatments given to cases of schizophrenia and depression, it was noted that the averages, given in Table VII, tended to conform fairly closely to opinions expressed by previous workers, e.g. Kalinowsky (17). However, it was considered that the questionnaire provided a good opportunity to ascertain the current practice on this controversial issue, so as to enable psychiatrists to have some form of base line from which to plan their treatments for these conditions.

Differences of opinion have been shown to exist in connection with almost every aspect of electro-convulsion therapy, and especially with regard to its

technique of administration. Opinions advocated by some are disfavoured by others, but the reasons for holding these opinions have been shown to be not entirely scientific, for in many instances they are founded upon subjective impressions and reports of single incidents (perhaps at other hospitals), or are based on hearsay. It was therefore considered that proper scientific data were urgently required, upon which to base a preference for a particular technique of E.C.T. These data can be obtained in two ways:

1. By a carefully controlled study, using a number of different techniques on the same patients, to determine which appears to be the most generally satisfactory, from the point of view of ease of administration, complications, patient's preference, etc. This is a fairly short-term project involving few staff but does not take into account any possible differences in therapeutic effectiveness between the different techniques. A scheme, conducted along these lines, has been in operation at this hospital during the past year, and will be reported later.

2. A longer term project involving more staff, using different groups of patients, in which an attempt would be made to investigate, amongst other things, any differences in the degree of recovery and the incidence of relapse following the use of different E.C.T. techniques. It would also be useful if this study could be extended to cover female as well as male patients.

#### SUMMARY

1. At a recent court case a number of psychiatrists failed to agree upon a uniform technique of electroplexy, as a result of which the plaintiff lost his case.

2. Previous writers presented a confusing picture concerning techniques of E.C.T. administration, and it was considered important to ascertain which techniques were in current practice at various mental hospitals and teaching centres in this country, and to obtain other useful data.

3. A questionnaire was sent out. This showed that opinions were sharply divided about the best technique of giving E.C.T. and whether an anaesthetist should or should not be in attendance. At some 60 per cent. of the hospitals contacted, E.C.T. was modified with Pentothal and Scoline, and at 85 per cent. relaxants were used. These findings were considered to be of value should any further cases of litigation arise.

4. The results were discussed in detail, and were taken to indicate the necessity for obtaining proper scientific data concerning the most satisfactory technique of giving E.C.T. A research scheme on these lines is at present in progress at Banstead Hospital. Future studies should include female as well as male patients.

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# THE RELATIONSHIP BETWEEN GLUCOSE TOLERANCE, BODY WEIGHT, AND CLINICAL STATE IN MELANCHOLIA

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IN a recent investigation the present author has shown that glucose tolerance (G.T.) was significantly lower in a group of middle-aged mental hospital patients suffering from severe depression, than in a non-psychiatric group of similar age distribution (Pryce, 1958). This observation is similar to many others reported earlier (see review by McFarland and Goldstein, 1939). The cause of this impairment of G.T. is unknown; it cannot be explained by defective absorption of glucose from the alimentary canal since an intravenous G.T. test was employed in the investigation mentioned. Again, defective dietary intake during the days before testing could have contributed to the decreased G.T. in only a few cases; there was also no correlation between G.T. and either general symptomatology or the patients' behaviour during testing. However, it was observed that the group of depressions weighed significantly less than the control group, though again no correlation was found between body weight and G.T. among the depressions themselves. McCowan and Quastel (1931) and others have reported a close parallel between decreased G.T. and "emotional tension", evidence which favours an emotional cause for the phenomenon, in line with the theories of W. B. Cannon (1911).

In the present investigation observations of G.T., body weight, and emotional state have been made in a group of depressions before and after treatment, in an attempt to clarify the relationship between them.

## METHOD AND MATERIALS

### *Experimental Group*

This consisted of 19 patients admitted to a mental hospital because of depression. Any patient admitted for this reason was considered eligible for study, provided there was no evidence of physical disease, apart from underweight. Of those accepted one was subsequently rejected because of mild diabetes, two proved too unco-operative for testing, and in one some injected glucose escaped perivenously and vitiated the test. Data on the 19 patients (17 women and 2 men) finally included are given in Table I. Case 5 was re-admitted 3 months after discharge and again studied (Case 14); a total of 20 pairs of observations was therefore obtained. The mean age, weight and height of the 18 female admissions on admission were  $56.8 \pm 2.53^*$  years,  $55.0 \pm 2.36$  Kg., and  $157.8 \pm 1.2$  cm. respectively. The clinical diagnoses given by the psychiatrists in charge of the cases were: involutional depression (11 cases), depression of manic-depressive type (2), endogenous depression (1), agitated melancholia with hysteria (1), depression with hysterical features (1), reactive

\* Mean value and standard error.

TABLE I

| Case            | Age<br>(years) | Height<br>(cm.) | Initial<br>Weight<br>(Kg.) | Diagnosis       | Length of<br>Illness | F.H. or P.H.<br>of Mental<br>Illness | No. of<br>E.C.T. | Days T <sub>2</sub><br>After<br>E.C.T. | Days<br>Between<br>Tests |
|-----------------|----------------|-----------------|----------------------------|-----------------|----------------------|--------------------------------------|------------------|----------------------------------------|--------------------------|
| 1               | 72             | 159             | 40.4                       | invol. dep.     | 3 months             | P.H.                                 | 4                | 5                                      | 15                       |
| 2               | 46             | 150             | 45.8                       | react. dep.     | 10 weeks             | —                                    | 5                | 14                                     | 28                       |
| 3 <sup>3</sup>  | 56             | 159             | 54.9                       | invol. dep.     | rec. 1 year          | —                                    | 4                | 12                                     | 25                       |
| 4               | 34             | 161             | 55.3                       | anx. + dep.     | 9 months             | F.H., P.H.                           | 6                | 50                                     | 68                       |
| 5               | 71             | 155             | 45.8                       | invol. dep.     | rec. 3 years         | F.H., P.H.                           | 5                | 10                                     | 35                       |
| 6               | 50             | 157             | 44.9                       | ag. mel. + hys. | 5 months             | —                                    | 6                | 15                                     | 36                       |
| 7               | 53             | 152             | 64.9                       | invol. dep.     | 7 months             | F.H., P.H.                           | 6                | 9                                      | 32                       |
| 8               | 62             | 152             | 62.6                       | invol. dep.     | 3-4 months           | F.H.                                 | 6                | 9                                      | 39                       |
| 9               | 62             | 163             | 60.8                       | invol. dep.     | months               | P.H.                                 | 6                | 14                                     | 35                       |
| 10              | 57             | 164             | 56.2                       | invol. dep.     | 3 weeks              | —                                    | 5                | 12                                     | 28                       |
| 11              | 55             | 152             | 45.4                       | invol. dep.     | 3 months             | F.H.                                 | 3                | 15                                     | 26                       |
| 12              | 63             | 159             | 72.1                       | dep. + hys.     | 3 months             | P.H.                                 | 5                | 19                                     | 39                       |
| 13              | 65             | 155             | 51.7                       | invol. dep.     | ? 2 weeks            | P.H.                                 | 7                | 17                                     | 44                       |
| 14              | 71             | 155             | 45.0                       | invol. dep.     | rec. 3 years         | F.H., P.H.                           | 3                | 19                                     | 28                       |
| 15              | 44             | 163             | 63.2                       | endog. dep.     | 3 months             | P.H.                                 | 6                | 16                                     | 37                       |
| 16              | 49             | 164             | 58.5                       | m-dep. dep.     | rec. years           | P.H.                                 | 3                | 13                                     | 20                       |
| 17 <sup>3</sup> | 58             | 161             | 69.4                       | m-dep. dep.     | 7-8 months           | P.H., ?F.H.                          | —                | —                                      | 21                       |
| 18              | 50             | 159             | 58.1                       | react. dep.     | 2 weeks              | P.H.                                 | —                | —                                      | 18                       |
| 19              | 52             | 161             | 73.9                       | react. dep.     | 4 months             | F.H.                                 | —                | —                                      | 43                       |
| 20              | 67             | 160             | 45.4                       | invol. dep.     | rec. 2 years         | F.H.                                 | —                | —                                      | 22                       |

dep.—depression; invol.—involuntal; react.—reactive; anx.—chronic anxiety state; ag. mel.—agitated melancholia; hys.—hysterical features; endog.—endogenous; m-dep.—manic-depressive; rec.—recurrent; P.H.—past history; F.H.—family history; T<sub>2</sub>—second observations.

depression (3) and chronic anxiety state with depression (1). In general a severe depression occurring for the first time after the age of 50 for no apparent reason was classified as either involuntal depression or according to symptomatology, e.g. "depression with hysterical features"; if the first attack occurred before the age of 50 it was "endogenous" or "manic-depressive psychosis"; and if the depression was related to an unpleasant experience in the patient's life, or proved to be strongly influenced by her environment, it was called "reactive". A family history of severe mental illness or suicide, or a past personal history of severe depression, or both, were present in 16 cases. Only 4 cases gave a history of illness lasting less than 3 months, and in one of these (Case 13) the information seemed unreliable.

Sixteen cases were treated with electrically induced convulsions; in each instance E.C.T. was administered after unconsciousness and muscular relaxation had been obtained with suitable intravenous doses of hexobarbitone and "Brevdil M". The average number of convulsions was  $5 \pm 0.26$ . Following the course of E.C.T. Case 4 received soluble insulin 40 u. daily for 3 weeks. Patients were interviewed regularly by their physicians, received sedatives when required, and attended occupational therapy classes when they began to improve; in 4 cases these measures alone were applied.

Observations of G.T., body weight and emotional state were first made soon after admission, before commencing E.C.T.; the same observations were made subsequently  $14 \pm 0.45$  days after the end of E.C.T. in those treated with E.C.T. However, in Case 1 the second observations were made 5 days after ending E.C.T., and in Case 4, 5 days after "modified" insulin therapy was discontinued. Excluding Cases 1 and 4 the interval between observations was  $31 \pm 1.8$  days.

### *Assessment of Emotional State*

Observations of posture, facial expression, speech, and thought content, and reports of subjective mood, were recorded on a check list before treatment; similar observations were made after treatment and each patient then graded as "Recovered" (entirely symptom-free), "Greatly improved" (evidence of some residual anxiety), "Slightly improved", and "Unimproved". "Recovered"



and "Greatly improved" patients showed large changes in emotional state. In each case the second assessment of emotional state was made before the second G.T. test. In 13 cases examined by the psychologist, the clinical judgments of outcome agreed with the results of psychological tests. In 8 cases the scores of the Minnesota Multiphasic Personality Inventory (M.M.P.I.) were obtained before and after treatment.

#### *Assessment of Glucose Tolerance*

No patient received a sedative during the 12 hours before testing, nor was any female patient menstruating. Careful enquiries were made from the nursing staff concerning dietary intake during the 4-5 days before testing; it had previously been shown that the ordinary hospital diet offered an adequate supply of carbohydrate (Pryce, 1958). For 4-7 days before the last 12 tests (Cases 13-16, 19, 20) the diet was supplemented with 100-150 g. glucose in orangeade daily. Records were kept of behaviour and pulse rate during testing.

The technique employed in 21 tests (Table II, Cases 1-7, 17, 18, 8(i), 9(i), 10(i)) has been described previously (Pryce, 1958). Two significant modifications were made in the remaining 19 tests. The molybdenum blue end colour used for colorimetric estimation was found to fade fairly rapidly (see also Lehmann and Silk, 1952); this could lead to appreciable error in reading 18 tubes. The phosphomolybdate reagent therefore was discarded in favour of the arsenomolybdate chromogen of Nelson (1944), which gives a very stable end colour, provided the reagents are well mixed and time allowed for the colour to develop. It was observed also that two Folin and Wu tubes frequently gave low readings; in these the "12.5 ml." gradation marks were found to contain 12.8 and 12.9 ml., whereas the other tubes were graduated accurately to within 0.1-0.2 ml. Thereafter the gradation marks were disregarded and equal volumes obtained by adding accurately measured volumes of reagents. The Folin and Wu tubes were not discarded in favour of ordinary test tubes sealed with cotton wool, since they had been found more efficient than the latter in preventing re-oxidation of the formed cuprous oxide. The effect of these two modifications will be described later. In the last 19 tests blood glucose concentration was measured by the method of Asatoor and King (1954), since this gives values more nearly approaching true blood-glucose concentration than the method of Folin and Wu (Harrison, 1949). Since, however, the G.T. index obtained is a measure of the rate of change of blood-glucose concentration this modification did not alter the value of the index.

Reasons have been given elsewhere for regarding the "total" index rather than the "increment" index as a more valid measurement of G.T. (Ikkos and Luft, 1957; Pryce, 1958). The "total" index (K) expresses the rate of fall of blood-glucose concentration as a constant percentage of total blood-glucose concentration at any time between 25 minutes from the beginning of injection and arrival at the fasting level, and is obtained from the slope of the straight line between log. blood-glucose concentration and time during this interval. Realization of the validity of the "total" index led to a further slight modification of technique after the first 18 tests (1-7, 17, 18) in that the first capillary blood sample was taken 10 minutes from "zero" (i.e. 17 minutes from beginning of injection), and further samples obtained at 5 minute intervals from "zero". (The original method was based on the intravenous test described by Duncan (1956) in which "zero" is taken as 4 minutes from the end of an injection lasting 3 minutes.) The index (K) was calculated graphically from the fitted

TABLE II

| Case | -b·100 |       | σb·100 |       | $\frac{\Delta b}{S_{\Delta b}}$ | D.F. | p      | K % per Minute |       | Signi-<br>ficant<br>Change<br>in K | Change<br>in<br>Weight<br>(Kg.) | Change<br>in Emo-<br>tional<br>State | M.M.P.I.<br>Depression<br>Scale |    |
|------|--------|-------|--------|-------|---------------------------------|------|--------|----------------|-------|------------------------------------|---------------------------------|--------------------------------------|---------------------------------|----|
|      | i      | ii    | i      | ii    |                                 |      |        | i              | ii    |                                    |                                 |                                      | i                               | ii |
| 1    | 0.393  | 0.364 | 0.064  | 0.018 | 0.44                            | 8    | >0.6   | 0.89           | 0.845 | O                                  | —                               | R                                    | 84                              | 47 |
| 2    | 0.848  | 0.519 | 0.072  | 0.059 | 3.24                            | 12   | <0.01  | 1.98           | 1.21  | —                                  | +5.0                            | R                                    | 87                              | 58 |
| 3    | 0.444  | 1.086 | 0.049  | 0.088 | 6.49                            | 12   | <0.001 | 1.05           | 2.47  | +                                  | +2.7                            | R—                                   |                                 |    |
| 4    | 0.304  | 0.308 | 0.048  | 0.051 | 0.22                            | 15   | >0.8   | 0.71           | 0.76  | O                                  | +2.3                            | O+                                   |                                 |    |
| 5    | 0.185  | 0.551 | 0.022  | 0.045 | 7.35                            | 14   | <0.001 | 0.42           | 1.28  | +                                  | +2.7                            | R                                    |                                 |    |
| 6    | 0.501  | 0.449 | 0.045  | 0.040 | 0.87                            | 12   | >0.4   | 1.16           | 1.04  | O                                  | +5.9                            | R—                                   | 72                              | 46 |
| 7    | 0.281  | 0.419 | 0.035  | 0.031 | 2.95                            | 14   | =0.01  | 0.67           | 0.96  | +                                  | O                               | R                                    | 79                              | 46 |
| 8    | 0.419  | 0.427 | 0.026  | 0.039 | 0.15                            | 15   | >0.8   | 0.96           | 0.98  | O                                  | +4.5                            | R                                    |                                 |    |
| 9    | 0.184  | 0.557 | 0.064  | 0.032 | 4.84                            | 15   | <0.001 | 0.42           | 1.26  | +                                  | +0.5                            | R—                                   | 92                              | 47 |
| 10   | 0.488  | 0.586 | 0.047  | 0.034 | 1.73                            | 12   | =0.1   | 1.16           | 1.31  | O                                  | -0.5                            | R                                    |                                 |    |
| 11   | 0.483  | 0.441 | 0.036  | 0.016 | 1.13                            | 16   | >0.2   | 1.12           | 1.02  | O                                  | +2.7                            | R—                                   | 73                              |    |
| 12   | 0.351  | 0.411 | 0.027  | 0.029 | 2.91                            | 17   | =0.01  | 0.83           | 0.94  | O                                  | -3.2                            | R—                                   |                                 |    |
| 13   | 0.449  | 0.437 | 0.016  | 0.058 | 0.25                            | 14   | =0.8   | 1.05           | 1.01  | +                                  | O                               | O+                                   |                                 |    |
| 14   | 0.426  | 1.059 | 0.011  | 0.047 | 16.89                           | 14   | <0.001 | 0.96           | 2.48  | +                                  | +4.5                            | R                                    | 51                              |    |
| 15   | 0.450  | 0.355 | 0.021  | 0.030 | 2.67                            | 17   | <0.02  | 1.04           | 0.825 | +                                  | +2.0                            | R—                                   | 97                              | 71 |
| 16   | 0.466  | 0.420 | 0.024  | 0.013 | 1.69                            | 18   | >0.1   | 1.08           | 0.98  | O                                  | +1.5                            | R—                                   | 94                              | 59 |
| 17   | 0.290  | 0.260 | 0.046  | 0.047 | 0.47                            | 13   | >0.5   | 0.69           | 0.59  | O                                  | O                               | O                                    | 77                              | 77 |
| 18   | 0.683  | 0.425 | 0.064  | 0.081 | 2.5                             | 14   | =0.025 | 1.59           | 0.99  | —                                  | +3.2                            | R—                                   |                                 |    |
| 19   | 0.548  | 0.676 | 0.019  | 0.024 | 4.17                            | 17   | <0.001 | 1.27           | 1.52  | +                                  | O                               | O                                    | 61                              |    |
| 20   | 0.322  | 0.367 | 0.024  | 0.020 | 1.51                            | 17   | >0.1   | 0.75           | 0.85  | O                                  | -4.1                            | O                                    |                                 |    |

R=recovered; R—=greatly improved; O+=slightly improved; O=no change.

regression line of log. blood-glucose concentration on time between 20 and 70 minutes, or between 20 minutes and arrival at the fasting level. Then  $K=0.693/t_f$ , where  $t_f$  is the time taken for blood-glucose concentration at any time to be halved (see Ikkos and Luft, 1957).

The weight of each subject was measured on Avery platform-scales; each subject was weighed with the same amount of clothing on the same scales on each occasion.

The statistical procedures described by Herdan (1955) were employed, together with the statistical tables of Fisher and Yates (1953). The formulae for small numbers of observations were used throughout. The significance of differences between values before and after treatment was assessed by the method for correlated means, since the patients acted as their own controls.

## RESULTS

### *Effect of Modification of Technique on the Measurement of G.T.*

Table II gives the values of the regression coefficients ( $-b$ ) and their standard deviations ( $\sigma b$ );  $-b \cdot 100$  is the tangent of the regression angle from which  $K$  was calculated. The mean value of  $-b \cdot 100$  in the 21 "unmodified" tests (1-7, 17, 18, 8(i), 9(i), 10(i)) is 0.448, and in the 19 "modified" tests it is 0.486; the difference (0.038) is not statistically significant ( $t=0.74$ ; D.F.=38;  $p>0.4$ ). The respective values of  $\sigma b \cdot 100$  are 0.050 and 0.027 and the difference (0.023) is highly significant ( $t=5.0$ ; D.F.=38;  $p<0.001$ ). Thus modification of technique had no effect on the value of  $b$ , but reduced its standard deviation by almost half. Now since the standard error ( $S_{\Delta b}$ ) of the difference ( $\Delta b$ ) between two values of  $b$  is determined by the magnitude of  $\sigma b$ , change in  $\sigma b$  affects the ratio  $\Delta b/S_{\Delta b}$  ( $=t$ ) and hence the significance of  $\Delta b$ . Nevertheless, with the values of  $\Delta b$  obtained, it can be shown that the effect of the greater value of  $\sigma b$  in the "unmodified" tests is negligible. Thus for  $p$  to be 0.05 then with 13 D.F. (mean D.F. for "unmodified" tests) and  $\sigma b$  of 0.05 in each test,  $\Delta b$  must be 0.114, while with 16 D.F. (mean D.F. for "modified" tests) and  $\sigma b$  of 0.027,  $\Delta b$  must be 0.079. In only one instance (Case 10) does  $\Delta b$  fall within the range 0.079-0.114; in all others  $\Delta b$  lies well outside this range. Modification of technique, therefore, had no effect on the measurement of G.T. and a negligible effect on the significance of the difference between two measurements; the less sensitive technique first used was therefore adequate for the purposes of the investigation. (The reasons for the larger observational error in the unmodified tests have been given earlier. Since the end-colours were read randomly, and the rate of fading is also unpredictable (Lehmann and Silk, 1952) it would be expected that fading would increase the random error. A systematic error was caused by the greater colour dilution in the two Folin and Wu tubes graduated faultily; values obtained from these tubes were therefore disregarded in calculating  $b$ , and the consequent fewer number of observations partly accounts for the higher  $\sigma b$  in the "unmodified" tests.)

### *Effect of Diet on G.T.*

If values of  $K$  under 1.2 per cent. per minute are regarded as probably abnormal, then in the 28 tests in which no glucose was added to the previous diet  $K<1.2$  per cent. per minute in 21 (75 per cent.); in the 12 tests in which the previous diet was supplemented with 100-150 g. glucose daily  $K<1.2$  per cent. per minute in 9 (75 per cent.). The respective mean values of  $b$  for these 21 and 9 tests are 0.373 and 0.410; the difference 0.037, is not significant



( $t=1.156$ , 28 D.F.,  $p>0.2$ ). Among the 21 tests are 4 in which the nursing staff reported the previous diet as "fair" (1(i), 9(i)), "decreased" (3(i)), and "very poor" (5(i)); the respective values for K are 0.89, 0.42, 1.05 and 0.42 per cent. per minute. As observed in the previous investigation (Pryce, 1958) the lowest values of K (0.42 per cent. per minute) are therefore among those few patients whose carbohydrate intake may have been inadequate during the days before testing. However, before all other tests (36) dietary intake was reported "normal", and as has been shown, the mean value of  $b$  ( $\equiv K$ ) could not be significantly increased by a substantial increase in the intake of carbohydrate. Low food intake during the days before testing is therefore likely to have been a factor reducing G.T. in only two instances (9(i), 5(i)).

*Effect of Treatment on G.T., Body Weight and Clinical State (Table II)*

The mean increase in K after treatment (0.175 per cent. per minute) is not significant ( $t=1.35$ , 18 D.F.,  $p=0.2$ ). The mean increase in body weight after treatment (1.56 Kg.) is significant ( $t=2.545$ , 17 D.F.,  $p=0.02$ ). After treatment 15 patients recovered or were greatly improved, and 5 were slightly improved or unimproved.

*Relationship Between Change in Clinical State and Change in G.T.*

Table III shows that there is no relationship between change in clinical state and change in G.T.; ( $\chi^2=0.073$ , 1 D.F.,  $p>0.7$ ). This is corroborated

TABLE III

|                           |      |    |    | Change in K |     |
|---------------------------|------|----|----|-------------|-----|
|                           |      |    |    | +           | O/— |
| Change in emotional state | R/R— | .. | .. | 6           | 9   |
|                           | O/O— | .. | .. | 1           | 4   |

See Table II for abbreviations.

by comparison of the mean decrease in the depression score of the M.M.P.I. with the mean change in G.T. values in the 7 patients who showed a decrease in their depression scores after treatment. The mean decrease in the depression scores (33) is highly significant ( $t=12.7$ , D.F.=5,  $p<0.001$ ), whereas the mean change in K (+0.19 per cent. per minute) is not significant ( $t=0.422$ , 5 D.F.,  $p>0.6$ ).

*Relationship Between Change in Body Weight and Change in G.T.*

Table IV shows that there is no relationship ( $\chi^2=2.24$ , 1 D.F.,  $p>0.1$ ). Moreover the Spearman rank correlation coefficient between change in K and change in body weight is  $-0.247$  ( $p>0.05$ ).

TABLE IV

|                  |     |    |    | Change in K |     |
|------------------|-----|----|----|-------------|-----|
|                  |     |    |    | +           | O/— |
| Change in weight | +   | .. | .. | 3           | 8   |
|                  | O/— | .. | .. | 4           | 4   |

*Effect of Length of Illness on G.T.*

The initial mean value of K in the 4 patients with a history of illness lasting less than 3 months is 1.44 per cent. per minute; this is greater than the initial

mean value (1.00 per cent. per minute) for the whole group and suggests that the relationship merits further investigation.

*Distribution of Values of G.T., and Analysis of Effect of Treatment on G.T.*

Figures 1, 2, 3 show the distribution of ranges of K before treatment, after treatment and for both groups combined. Values of  $K < 1.2$  per cent. per minute are found in 17 cases (85 per cent.) before treatment, and in 13 cases (65 per cent.) after treatment; the difference in frequency is not statistically significant ( $\chi^2 = 1.2$ , 1 D.F.,  $p > 0.2$ ). The histogram for the combined groups is fairly uniform, with its apex around 1.0 per cent. per minute, a gradual fall to the right into the normal range of G.T. and a more abrupt fall to the left; the distribution is therefore skewed to the left. It has been shown that the two lowest values of K are probably due to a low food intake; if these are excluded, the skewness is exaggerated.

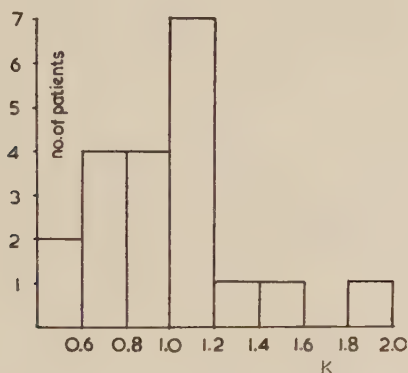


FIG. 1.—Distribution of K before treatment.

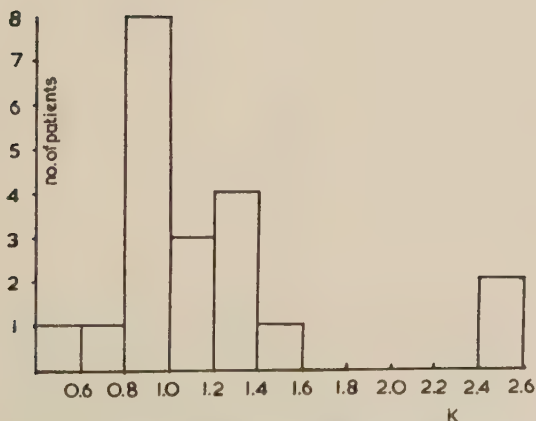


FIG. 2.—Distribution of K after treatment.

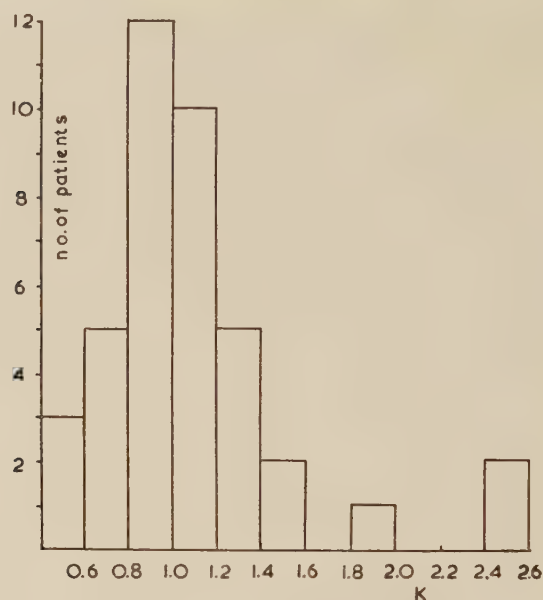


FIG. 3.—Distribution of K in the combined groups.

One of the most remarkable observations in this investigation are two extremely high values of K (2.48 per cent. per minute) after treatment; these are quite separate from the other values and are above the upper limit of normality given in the literature (Amatuzio *et al.*, 1953; Duncan, 1956); Figure 4 illustrates one of the two cases; the significance of this finding will be

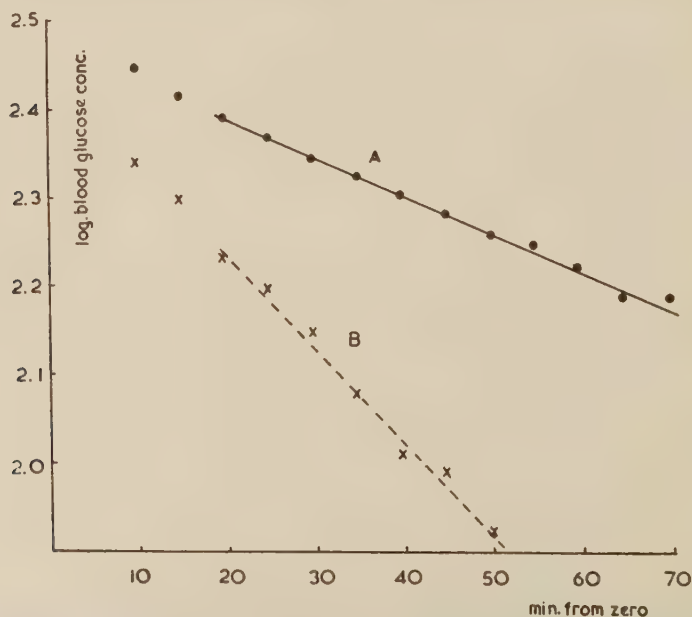


FIG. 4.—Case 14. A—before treatment ( $K=0.96$  per cent. per minute); B—after treatment ( $K=2.48$  per cent. per minute).



discussed later. In the 17 cases with initial values of  $K < 1.2$  per cent. per minute, 10 showed no significant change in G.T. after treatment; 6 showed an increase and 1 a decrease in G.T.; in the 3 with initial  $K > 1.2$  per cent. per minute, G.T. was significantly decreased in 2 and increased in 1. An initially low G.T. value, therefore, tended to remain stable or to increase, while the few initially "normal" G.T. values seemed unstable.

### *Behaviour and Pulse Rate During the G.T. Test*

The relevant data were not obtained for Case 1; nor was pulse rate obtained for 2(i). Behaviour is described as "still and quiet" in 30 tests, "a little restless" or "a little agitated" in 2(i), 6(i), 19(i), 20(i) and (ii), "co-operative but excited and somewhat restless at the prospect of discharge" in 2(ii), "agitated" in 10(i), and "very restless" in 13(i). The mean value of  $K$  in the 8 instances of increased motor activity during testing is 1.18 per cent. per minute, which is greater than the mean value (1.06 per cent. per minute) for the whole group; increased motor activity is therefore unlikely to have been a factor decreasing G.T. The mean pulse rate during the first test was 79/minute; during re-testing 73/minute; the mean pulse rate difference ( $-4.5$ /minute) is barely significant ( $t=2.085$ , 16 D.F.,  $t_{(p=0.05)}=2.120$ ) (Table V).

TABLE V

| Case       | Mean Pulse Rate |    | Fasting Blood Glucose<br>(mg. per cent.) |     |
|------------|-----------------|----|------------------------------------------|-----|
|            | i               | ii | i                                        | ii  |
| 1 .. .. .  | —               | —  | 113                                      | 87  |
| 2 .. .. .  | —               | 60 | 92                                       | 107 |
| 3 .. .. .  | 68              | 64 | 87                                       | 85  |
| 4 .. .. .  | 86              | 76 | 109                                      | 100 |
| 5 .. .. .  | 74              | 80 | 110                                      | 115 |
| 6 .. .. .  | 82              | 60 | 121                                      | 84  |
| 7 .. .. .  | 80              | 88 | 117                                      | 104 |
| 8 .. .. .  | 80              | 72 |                                          |     |
| 9 .. .. .  | 86              | 78 |                                          |     |
| 10 .. .. . | 70              | 62 |                                          |     |
| 11 .. .. . | 70              | 82 | 84                                       | 103 |
| 12 .. .. . | 92              | 88 | 103                                      | 101 |
| 13 .. .. . | 116             | 98 | 107                                      | 127 |
| 14 .. .. . | 72              | 81 | 100                                      | 86  |
| 15 .. .. . | 78              | 70 | 99                                       | 92  |
| 16 .. .. . | 70              | 60 | 107                                      | 103 |
| 17 .. .. . | 78              | 68 | 125                                      | 126 |
| 18 .. .. . | 64              | 60 | 115                                      | 112 |
| 19 .. .. . | 72              | 76 | 96                                       | 121 |
| 20 .. .. . | 76              | 70 | 87                                       | 90  |

### *Fasting Blood Sugar*

The mean values before and after treatment are given in Table V (Cases 8–10 are excluded because the method of estimating blood sugar differed on re-testing). The mean difference on re-testing ( $-1.7$  mg. per cent.) is not significant ( $t=0.432$ , 15 D.F.,  $p>0.6$ ). However, it should be noted that in 5 cases (1, 6, 11, 13, 19) the difference on re-testing exceeded 15 mg. per cent. which is three times the expected experimental error.

*Comparison of Present Data with Those from the Previous Investigation (Pryce, 1958) (Table VI)*

TABLE VI

|                                  | Present Investigation  |                      | Previous Investigation |              |
|----------------------------------|------------------------|----------------------|------------------------|--------------|
|                                  | A                      | B                    | C                      | D            |
|                                  | Before Treatment (18)* | After Treatment (18) | Depressions (17)       | Controls (9) |
| K % per min. ..                  | 1.00 ± 0.090           | 1.125 ± 0.092        | 1.09 ± 0.039           | 1.60 ± 0.10  |
| Body wt. (Kg.)                   | 55.0 ± 2.36            | 57.4 ± 2.15          | 54.6 ± 1.80            | 67.6 ± 2.7   |
| Height (cm.) ..                  | 157.8 ± 1.2            |                      | 159.4 ± 2.4            | 158.9 ± 2.15 |
| Age (years) ..                   | 56.8                   |                      | 57.4                   | 61.1         |
|                                  |                        | Difference           | t                      | D.F.         |
| K per cent. per minute (G.T.) .. |                        | A — C                | 0.9                    | 33           |
|                                  |                        | B — C                | 0.35                   | 33           |
|                                  |                        | A — D                | 4.48                   | 25           |
|                                  |                        | B — D                | 3.58                   | 25           |
| Body weight .. .. .              |                        | A — C                | 0.13                   | 33           |
|                                  |                        | B — C                | 1.0                    | 33           |
|                                  |                        | A — D                | 3.27                   | 25           |
|                                  |                        | B — D                | 2.88                   | 25           |
| Height .. .. .                   |                        | AB — C               | 0.615                  | 33           |
|                                  |                        | AB — D               | 0.487                  | 25           |
|                                  |                        |                      |                        | p            |
|                                  |                        |                      |                        | > 0.3        |
|                                  |                        |                      |                        | > 0.7        |
|                                  |                        |                      |                        | < 0.001      |
|                                  |                        |                      |                        | < 0.001      |
|                                  |                        |                      |                        | > 0.8        |
|                                  |                        |                      |                        | = 0.3        |
|                                  |                        |                      |                        | < 0.01       |
|                                  |                        |                      |                        | < 0.01       |
|                                  |                        |                      |                        | > 0.5        |
|                                  |                        |                      |                        | > 0.6        |

\* No. of subjects.

The two groups of depressions and the control group are of similar height and age distribution. Apart from the difference in body weight between groups A and B, there is no statistical difference in G.T. or in body weight among the groups of depressions, A, B, and C. G.T. and body weight are, however, significantly lower in groups A, B and C, than in the control group D.

## DISCUSSION

The interval between pre- and post-treatment measurements was mainly determined by the necessity of obtaining a rapid turnover of patients in the hospital, an object largely realized by the early discharge of patients suffering from depression who had improved or recovered. In practice, however, the interval proved sufficiently long to allow unequivocal and significant changes in all three variables observed (G.T., body weight and clinical state) in varying proportions of the experimental group. Indeed, a longer interval, by allowing "improvement" in each variable throughout the group, might have been less informative.

Although it is known that E.C.T. can cause an immediate transient hyperglycaemia, its delayed effect on G.T. is uncertain. Glynn (1945) in a short communication states that oral G.T. curves show increasing abnormality after 2-6 convulsions, and that only when the mental state has been normal for many weeks do the G.T. curves become normal. Aldrich (1948) in a study of 102 acute schizophrenics found no clear relationship between G.T. (as determined by the Exton-Rose test) and the effect of E.C.T. Freeman and Zaborenke (1949) again with the Exton-Rose test, studied G.T. twice before and then at monthly intervals during E.C.T. in a group of psychotic patients; no change in G.T. was found in schizophrenics, while all other groups showed "some improvement". In the present investigation among the 16 patients treated with E.C.T., G.T. was increased in 6, decreased in 2, and unchanged in 8; the mean value of b ( $\equiv$ K) after treatment with E.C.T. (14 cases, excluding 3(ii) and 14(ii)) is

0.446, which is not significantly different from 0.432, the mean value of  $b$  for the retests on the 4 patients not treated with E.C.T.; again the mean value of  $b$  for the retests on the 2 cases each given 3 convulsions (Case 14(ii) excluded) is 0.430, which is not significantly different from 0.467, the mean retest value for the 6 cases each given 6 or 7 convulsions. There is no evidence, therefore, that E.C.T. had any delayed effect on G.T. in the present investigation.

The mean weight gain (1.56 Kg.) observed could be entirely due to the increase in volume of extracellular water known to occur in treated psychotics (Altschule and Tillotsen, 1948-49). Crammer (1957) also observed rapid weight changes (presumed due to changes in volume of extracellular water) of up to 4 Kg. in psychotic patients. The weight increases of the order observed in the present investigation, therefore, probably do not signify improvements in nutritional state. If this is true, the question arises whether the food supply was sufficient to allow the formation of new tissue in patients most of whom were, in fact, underweight. As described earlier, difficulty in feeding an adequate diet was reported in only 4 patients; the failure to gain "real" weight in the majority, therefore, remains a problem. Detailed nutritional studies with determinations of extracellular space are needed to clarify the matter. Whatever new facts emerge, the present results indicate that it is unlikely that G.T. and nutritional state are intimately correlated.

Early in the century (1911) Cannon *et al.* described emotional glycosuria in animals; they showed that it did not occur when the adrenal glands were removed, and suggested that it was caused by adrenaline secreted in preparation for "fight or flight". These observations and theory have exerted a widespread influence on the interpretation of decreased G.T. in mental illness. Kooy in 1919 seems to have been the first to apply Cannon's views to the psychiatric problem, and as recently as 1955 Rames and Simon evoked them in explanation of their experimental results. The "emotion-adrenaline theory", as it may be called, implies that unpleasant emotions are accompanied by nervous stimulation of the adrenal medulla (or by general sympathetic activity) which leads to release of adrenaline into the blood stream which causes hyperglycaemia by hepatic glycogenolysis. This attractive theory has been attacked from many quarters. Mann (1925) considered that the hyperglycaemia produced by emotion or adrenaline was too small to account for the observed decrease in G.T. On reviewing the literature, Bowman and Kasanin (1929) found that the evidence for emotional glycosuria and hyperglycaemia was conflicting; moreover in 148 cases of mental illness they found no correlation between fasting blood-sugar values and diagnosis, type or intensity of mood. Freeman *et al.* (1944) observed that the decreased G.T. in 70 per cent. of 91 soldiers discharged on psychiatric grounds was unaccompanied by rise in pulse rate or B.P., unlike the decreased G.T. they produced by giving parenteral adrenaline; they also observed normal fasting blood-sugar values, which would not occur they said in the presence of excess blood adrenaline. More recent work, however, lends the theory some support. Among the various categories of mental illness, Weil-Malherbe (1955) found the highest concentration of plasma adrenaline in melancholics, although the values were not statistically significantly higher than normal. It is generally agreed that G.T. is decreased most frequently in this psychiatric group. Weil-Malherbe's additional observation (1955) that sedatives lower the concentration of blood adrenaline could on the "emotion-adrenaline theory" also explain an observation made by Tod in 1935, that sedatives improve G.T. when this is impaired in mental illness. However barbiturates, the sedatives used by Weil-Malherbe and Tod, are said to block



or modify the release of corticotropin (Harris, 1955), and therefore may also lower the blood level of adrenal glucocorticoids, other metabolites which decrease G.T.

Fundamental to the "emotion-adrenaline" theory as it stands is the demonstration of a close relationship between emotional state and G.T. More than one author has reported such a relationship, but the data are not convincing. McCowan and Quastel (1931), using a somewhat arbitrary measure of G.T., the "hyperglycaemic index" (HI), stated that they found the closest parallel between the magnitude of the HI and the "emotional tension" of the patient. Apart from criticisms of the HI (see Katzenelbogen and Friedman-Buchman, 1933), the authors describe the emotional state of only three "illustrative" cases, and explain the normal or nearly normal HI values in 10 of their 43 depressions as due to "hysteriform features". Tod (1936) repeating the work came to the same conclusion, but he again confined description of each patient's emotional state to two or three adjectives. When Tod and Jones (1937) measured the HI in 20 cases of acute and subacute anxiety states they failed to find a relationship between G.T. and emotional state, and assumed that this was somehow related to a difference between anxiety and melancholy. Holmgren and Wohlfahrt (1944) studied the effect of repeated injections of adrenaline on the mean blood-sugar value (B) of psychiatric patients and normal controls, scoring "affectivity" by means of a rating scale. They found that the B values ran parallel with "affectivity", but disclaimed that one was dependent on the other. Moreover, it is difficult to see how G.T. is related to the mean blood-sugar value after repeated injections of adrenaline.

In 1933, Katzenelbogen and Friedman-Buchman reported on G.T. tests in 134 psychiatric patients, and suggested that the high percentage of curves indicating decreased G.T. was due to emotional tension. Two years later Katzenelbogen and Muncie (1935) performed G.T. tests on 50 patients, and also made careful concurrent observations of type and intensity of emotional reactions using detailed behaviour charts. Contrary to their expectation, no correlation was, in fact, observed between G.T. and emotional state. In the present investigation reliance was placed on the large changes in emotional state commonly effected by E.C.T. in depressions, and as previously described, no correlation was found between emotional state and G.T. The results of these investigations, together with the unsatisfactory nature of the evidence in favour of a correlation between the two variables, and the other criticisms mentioned, indicate that a simple explanation of the decreased G.T. in terms of the "emotion-adrenaline theory" is untenable.

It is possible, however, that the defect in carbohydrate metabolism may be more intimately linked with the activity of the cortex of the adrenal gland. As yet there are no reports of the relationship between glucocorticoid secretion and G.T., probably because methods of estimating plasma and urinary glucocorticoids have only recently been evolved. There is, however, circumstantial evidence to support the theory that increased glucocorticoid secretion may account for the observed decreased G.T. Board *et al.* (1957) report significantly higher blood-hydrocortisone levels in 33 patients with depressive reaction than in normal people, with significantly higher values in the more depressed than in the less depressed. Weil-Malherbe and Bone (1951) report inhibition of the hexokinase reaction by plasma from melancholics with decreased G.T., and suggest that the inhibitory factor may be an adrenocortical hormone. However, if this theory proves correct, the situation is likely to be complex. It is known that a prolonged raised blood-glucocorticoid level leads to a compensatory

increase in insulin secretion and even to pancreatic hypertrophy (Thorn *et al.*, 1957; Demanet *et al.*, 1958). The resulting G.T., therefore, reflects the balance between two opposing influences. One may surmise that before the establishment of hormonal equilibrium G.T. may be liable to wide fluctuations which would, however, explain the instability of the initially "normal" G.T. values reported in the present investigation. Moreover, during recovery, cessation of excessive glucocorticoid secretion might precede cessation of the compensatory increase in secretion of insulin, giving a period during which G.T. is actually increased above normal; such a mechanism would explain the two excessively high values after treatment observed here. In long-standing illnesses (as were most of the present cases) the adrenal cortex might hypertrophy, so that cessation of the original stimulus to increased adrenocortical activity would not lead to an immediate decrease in glucocorticoid secretion; the patient might, therefore, show other signs of recovery before his G.T. returned to normal, an assumption which again would explain many of the present results. Finally, the stimulation of gluconeogenesis by excessive glucocorticoid secretion might also in part account for the observed loss of weight, as in Cushing's syndrome (Thorn *et al.*, 1957).

#### SUMMARY

G.T., body weight and emotional state were observed before and after treatment in 20 subjects admitted to a mental hospital because of depression. No correlation was observed between change in G.T. after treatment and either change in weight, or change in emotional state. The significance of these findings is discussed, and in particular it is shown that decreased G.T. in depression cannot be due to current emotional disturbance. An alternative theory is suggested.

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# PSYCHOLOGICAL EFFECTS OF CENTRALLY ACTING DRUGS IN MAN

## EFFECTS OF CHLORPROMAZINE AND SECOBARBITAL ON VISUAL AND MOTOR BEHAVIOUR

By

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IN a previous study (Kornetsky, Humphries and Evarts, 1957) it was found that the impairment of a variety of psychological processes caused by 200 mg. of chlorpromazine was not significantly less than the impairment produced by 200 mg. of secobarbital. It was also shown that the effects of drugs on psychological performance in man are related not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject. It appeared that there was something unique to the individual which accounted for a significant portion of the effect of a drug. The present study was designed to extend these observations by reducing the number of drugs tested (in the previous study four drugs were used) and increasing the number of times a subject received each drug. It was hoped that this would give a better estimate of the effect of a specific dose of a specific drug and thus decrease the error of measurement and increase the reliability of the correlation between drugs.

### METHODS

Twelve normal volunteers between the ages of eighteen and thirty, five males and seven females, served as subjects. All subjects received the following drugs at the dosages indicated:

- |                                 |                 |
|---------------------------------|-----------------|
| 1. Chlorpromazine hydrochloride | 100 and 200 mg. |
| 2. Secobarbital sodium          | 100 and 200 mg. |

Each drug at each dose was given twice so that the subjects received drugs on a total of eight days. In addition to the drugs, placebos were given on two separate days. There was also one control day prior to the start of the experiment and another at the completion of the experiment. The experimental design employed is shown in Table I. There was a minimum of one day between drug treatments. All drugs, including placebos, were administered orally in identical capsules. Subjects did not eat breakfast on mornings that drugs were to be given. The "double-blind" technique was employed throughout.

TABLE I  
Experimental Design

| Subject |    |    | Day  |     |   |     |     |     |     |   |     |     |
|---------|----|----|------|-----|---|-----|-----|-----|-----|---|-----|-----|
|         |    |    | 1    | 2   | 3 | 4   | 5   | 6   | 7   | 8 | 9   | 10  |
| A       | .. | .. | C-1* | S-2 | P | S-1 | C-2 | S-2 | C-1 | P | C-2 | S-1 |
| B       | .. | .. | C-2  | S-1 | P | S-2 | C-1 | S-1 | C-2 | P | C-1 | S-2 |
| C       | .. | .. | S-2  | C-1 | P | C-2 | S-1 | C-1 | S-2 | P | S-1 | C-2 |
| D       | .. | .. | S-1  | C-2 | P | C-1 | S-2 | C-2 | S-1 | P | S-2 | C-1 |
| E       | .. | .. | C-1  | S-1 | P | C-2 | S-2 | S-2 | C-2 | P | S-1 | C-1 |
| F       | .. | .. | C-2  | S-2 | P | C-1 | S-1 | S-1 | C-1 | P | S-2 | C-2 |
| G       | .. | .. | S-1  | C-1 | P | S-2 | C-2 | C-1 | S-1 | P | C-2 | S-2 |
| H       | .. | .. | S-2  | C-2 | P | S-1 | C-1 | C-2 | S-2 | P | C-1 | S-1 |
| I       | .. | .. | C-1  | C-2 | P | S-2 | S-1 | C-2 | C-1 | P | S-1 | S-2 |
| J       | .. | .. | C-2  | C-1 | P | S-1 | S-2 | C-1 | C-2 | P | S-2 | S-1 |
| K       | .. | .. | S-1  | S-2 | P | C-2 | C-1 | S-2 | S-1 | P | C-1 | C-2 |
| L       | .. | .. | S-2  | S-1 | P | C-1 | C-2 | S-1 | S-2 | P | C-2 | C-1 |

\* C-1: Chlorpromazine, 100 mg.; C-2: Chlorpromazine, 200 mg.; S-1: Secobarbital, 100 mg.; S-2: Secobarbital, 200 mg.; P: Placebo.

Ninety minutes after the administration of the drug, the following behavioural measures were obtained:

1. *A Modified Digit Symbol Test*: This test is generally similar to that in the Wechsler-Bellevue test (Wechsler, 1944) of adult intelligence. In order to minimize learning a different code was used each time the subject received the test.

2. *Pursuit Rotor*: A standard Gerbrands machine rotating at 30 r.p.m. was used. The subject was required to maintain contact between a stylus held in the hand and a small electrical contact on the rotating turntable. Subjects were given sixteen trials of thirty seconds each. Eight of the trials were done under a mild shock motivation. The shock intensity was 1.9 milliamperes. The time of contact was recorded for each trial and the means for both motivated and unmotivated conditions were recorded.

3. *Hand Steadiness*: Subjects were required to hold a stylus in holes of various diameters for 10 seconds each. There were five holes ( $\frac{1}{2}$  inch,  $\frac{5}{8}$  inch,  $\frac{1}{4}$  inch,  $\frac{3}{8}$  inch and  $\frac{5}{16}$  inch in diameter) and subjects were given two trials on each hole, one motivated and one unmotivated. In the motivated trials subjects received a mild electric shock to the fingers of the left hand when the stylus made contact with the side of the hole. Score was the mean time in contact. The greater the score the poorer the performance.

4. *Tapping Speed*: Subjects were required to tap as quickly as possible with a stylus on a metal plate. Five trials of ten seconds each were recorded. Score was the mean number of taps for the five trials.

5. *Tachistoscopic Recognition of Numbers*: A modification of the Dodge tachistoscope (manufactured by Gerbrands) was used. Subjects were presented with a series of numbers consisting of from one digit to six digits at exposure speeds of .01 second up to the exposure time necessary for the subject to get three consecutive numbers of six digits correct. Exposure was increased at steps of .02 second at a time. The score was the total number of errors.

At the completion of these tests, which lasted approximately one hour, subjects were allowed to rest for five minutes in a supine position. At this time a nurse recorded blood pressure, pulse, respiration, and oral temperature. Starting four hours after the administration of the drug, for a total of 17 hours,

nurses recorded whether the subject was asleep. The score was the total number of hours asleep during the seventeen hour period.

*Treatment of Data:* An analysis of variance (Edwards, 1946) was computed from the data for each test. The significance of differences between the effects of the drugs and the effects of the placebos was obtained by means of the single-tailed Dunnett *t*-test (Dunnett, 1955). Since a previous experiment (Kornetsky *et al.*, 1957) had indicated that both chlorpromazine and secobarbital impair functioning, there was no expectation that these two drugs would improve functioning in the present experiment; thus a single-tailed test was justified. The test of significance of differences between the effects of drugs was computed by means of the Scheffé test (Scheffé, 1953). To test whether or not the subjects who were most affected by one drug were also most affected by the other drugs, the product moment correlation (Edwards, 1946, p. 79) was computed and then the control score level was partialled out by means of partial correlations (Edwards, 1946, p. 125).

## RESULTS

*Psychological effects:* In every case the analysis of variance F ratio was significant for subjects, tests and drugs. Table II shows the mean score for all

TABLE II  
*Mean Scores on All Tests for All Experimental Conditions*

| Test                                                  |         |         | Chlorpromazine |        | Secobarbital |        |
|-------------------------------------------------------|---------|---------|----------------|--------|--------------|--------|
|                                                       | Control | Placebo | 100            | 200    | 100          | 200    |
| Digit symbol .. .. .<br>(No. correct)                 | 69.5    | 69.2    | 65.6           | 63.1*  | 68.0         | 58.5*  |
| Hand steadiness<br>(in seconds)                       | .38     | .29     | .55*           | .93*   | .29          | .32    |
| Tapping speed<br>(No. of taps)                        | 78.5    | 78.2    | 73.9*          | 70.2*  | 77.6         | 73.7*  |
| Pursuit rotor .. .. .<br>(Time in contact in seconds) | 24.47   | 24.60   | 19.60*         | 14.93* | 24.26        | 22.00* |
| Tachistoscopic<br>(No. of errors)                     | 21.79   | 12.67   | 17.83          | 50.92* | 14.88        | 16.29  |
| Sleep time .. .. .<br>(Median hours)                  |         | 1.0     | 4.5*           | 8.0*   | 0.5          | 2.0    |

\* Significant difference from placebo ( $p < .05$ ).

subjects on each test for each drug and dose. The Dunnett *t*-test was used to test the significance of the differences between the scores on each drug and dose with the placebo score. Since there were no significant differences between motivated and unmotivated conditions for the Pursuit Rotor and the Hand Steadiness tests, the motivated and unmotivated conditions were combined for each test. Since a balanced design was employed, day 1 and day 2 on the same dosage of a given drug were combined in computing mean effects without biasing the results.

Two hundred mg. of chlorpromazine produced a significant impairment of performance on the tests of Digit Symbol, Hand Steadiness, Tapping Speed, Pursuit Rotor, and Tachistoscopic Threshold. One hundred mg. of chlorpromazine produced significant impairment of performance on the tests of Hand Steadiness, Tapping Speed, and Pursuit Rotor.



Two hundred mg. of secobarbital caused significant impairment of performance on the Digit Symbol, Tapping Speed, and Pursuit Rotor tests. One hundred mg. of secobarbital caused no significant impairment of performance on any of the tests.

A comparison between the effects of each of the drugs at each of the two doses was carried out by means of the Scheffé test. This comparison indicated that on the Digit Symbol test 200 mg. of secobarbital produced significantly greater impairment in performance ( $p < .05$ ) than either 100 mg. of secobarbital or 100 or 200 mg. of chlorpromazine.

On the Hand Steadiness test 200 mg. of chlorpromazine caused significantly greater impairment ( $p < .05$ ) than any of the other drugs. One hundred mg. of chlorpromazine produced significantly greater impairment ( $p < .05$ ) than either 100 or 200 mg. of secobarbital.

On the Tapping Speed test 200 mg. of chlorpromazine caused greater impairment of performance than any of the other drugs ( $p < .05$ ). There was no significant difference in the degree of impairment of performance after 200 mg. of secobarbital and 100 mg. of chlorpromazine. Both these drugs at 200 mg. and chlorpromazine at 100 mg. dosage, respectively, produced greater impairment than 100 mg. of secobarbital ( $p < .05$ ).

On the Pursuit Rotor test, 200 mg. of chlorpromazine produced significantly greater impairment ( $p < .05$ ) of performance than any of the other drugs. One hundred mg. of chlorpromazine caused significantly greater impairment of performance on this test ( $p < .05$ ) than 200 and 100 mg. of secobarbital. Two hundred mg. of secobarbital caused significantly greater impairment ( $p < .05$ ) than 100 mg. of secobarbital.

On the Tachistoscopic Threshold test 200 mg. of chlorpromazine caused significantly greater impairment ( $p < .05$ ) of performance than any of the other drugs. On this test, no other drugs caused significant impairment.

Table II also shows the mean number of hours slept by each subject during the period of between 4 and 21 hours after the administration of the drug. Using the Mood Median test (Mood, 1950, p. 398) a  $\chi^2$  of 37.9 was obtained. Only 200 and 100 mg. of chlorpromazine produced significantly greater sleep time than the other drugs (including placebo).

In order to test the hypothesis that subjects who are most affected by one drug are also most affected by the other drugs, the Pearson Product Moment correlation was computed between the effects of each drug and the effects of all the other drugs. The original ability of the subjects was partialled out by means of partial correlations. This was done for each test used. Table III shows

TABLE III  
*Mean Partial Correlations of all Experimental Treatments for Each Test*

|          | Tapping<br>Speed | Hand<br>Steadiness | Digit<br>Symbol | Pursuit<br>Rotor | Tachistoscopic<br>Threshold |
|----------|------------------|--------------------|-----------------|------------------|-----------------------------|
| Mean ..  | .516             | .570               | .512            | .439             | .120                        |
| Range .. | .237-.680        | .286-.894          | 0.64-.848       | -.015-.785       | -.348-.663                  |

the means of these partial correlations for each test. In all but one case these mean correlations were substantial (.44 to .57). The exception was that computed from the tachistoscopic perception test (.12).

*Physiological effects:* Only temperature and pulse yielded a significant analysis of variance F ratio for drug treatments and in both cases 100 and 200

mg. of chlorpromazine produced a significant effect under the conditions of the experiment. Table IV shows the mean physiological values for each drug.

TABLE IV  
*Mean Changes in Systolic Blood Pressure, Respiratory Rate, Pulse  
and Oral Temperature*

| Sign                        | Chlorpromazine |         | Secobarbital |         | Placebo |
|-----------------------------|----------------|---------|--------------|---------|---------|
|                             | 100 mg.        | 200 mg. | 100 mg.      | 200 mg. |         |
| Blood pressure <sup>a</sup> | 111.42         | 112.00  | 107.62       | 107.50  | 109.42  |
| Respiration <sup>b</sup> .. | 17.25          | 18.00   | 18.17        | 18.92   | 18.33   |
| Pulse <sup>b</sup> ..       | 73.17*         | 75.25*  | 65.67        | 67.00   | 65.75   |
| Temperature <sup>c</sup> .. | 36.24†         | 36.05†  | 36.48        | 36.49   | 36.63   |

\*  $P < .05$  between score and placebo score.

†  $P < .01$  between score and placebo score.

<sup>a</sup> mm. of mercury.

<sup>b</sup> per minute.

<sup>c</sup> degrees centigrade.

#### COMMENT

The results of this experiment indicate that in most tasks involving motor co-ordination 100 mg. of chlorpromazine causes greater impairment of performance than 200 mg. of secobarbital. However, in a task that is related to intellectual function (Digit Symbol) 200 mg. of secobarbital produced significantly greater impairment than 200 mg. of chlorpromazine, although the latter did cause significantly more impairment than the placebo. Perception as measured by the tachistoscopic threshold was affected only by 200 mg. of chlorpromazine. In the previous study (Kornetsky, Humphries and Evarts, 1957) secobarbital appeared to have greater effects on intellectual function than chlorpromazine and about the same effects on a motor task (Pursuit Rotor). These differences were not statistically significant. In the present study, in which each dose of the drug was repeated, significant differences were found between the effects of chlorpromazine and secobarbital. Chlorpromazine caused greater impairment of performance than did secobarbital.

In order to determine if the differences in effects between chlorpromazine and secobarbital could have been caused by the shorter duration of action of secobarbital a brief additional experiment was performed. In this experiment eight subjects were tested seven times on Tapping Speed and the Digit-Symbol test in a 170-minute period immediately after receiving 200 mg. of secobarbital. Table V shows the times of testing and results of this experiment for both

TABLE V  
*Effects on Digit Symbol Test and Tapping Speed Test at Various Times  
after Secobarbital Administration*

| Time since drug adminis-<br>tration (in minutes) | .. | 5-25  | 30-50 | 55-75 | 80-100 | 105-125 | 130-150 | 155-175 |
|--------------------------------------------------|----|-------|-------|-------|--------|---------|---------|---------|
| Digit symbol ..                                  | .. | 94.1* | 67.2  | 67.8  | 77.2   | 79.3    | 87.1    | 90.0    |
| Tapping speed ..                                 | .. | 94.0  | 78.2  | 78.8  | 83.3   | 85.7    | 87.5    | 90.0    |

\* Per cent. of control values.

Tapping Speed and the Digit-Symbol test. As can be seen the maximum effect is reached between 55 and 75 minutes after the drug and is still quite marked up to 125 minutes. In the main experiment all testing was done between 90 and 120 minutes after the drug was administered so that it is unlikely that the differences found between secobarbital and chlorpromazine could be the result

of testing after the effects of secobarbital had worn off. Also, in the main experiment the Digit-Symbol test was administered immediately following the Tapping Speed test. The former takes 90 seconds to complete and the latter approximately five minutes.

The differences in effects between chlorpromazine and secobarbital can possibly be explained merely as a function of differences in dose. This explanation would be most parsimonious if chlorpromazine had a greater effect than secobarbital on all the various tests; however, the reversal of effects found on the Digit-Symbol test indicates that at the doses of the drugs used, secobarbital does have a greater effect on the Digit-Symbol test than chlorpromazine and a lesser effect on the motor tasks. Obviously, if the dose of secobarbital was increased it is very likely that the effects on these other tasks would be as great as the effects of chlorpromazine; however, this would also increase the difference in effect of the two drugs on the Digit-Symbol test.

At the present time it cannot be stated that the same results would be obtained if the drugs were administered chronically. There is, indeed, evidence that tolerance does develop to both chlorpromazine and secobarbital. Also, it cannot be categorically concluded that schizophrenic patients (as contrasted to normal controls) who receive acute dosages of chlorpromazine would be equally impaired. It has been reported (Kovitz, Carter and Addison, 1955) that there is an improvement in intellectual performance of schizophrenic patients after the administration of chlorpromazine. Shaten *et al.* (Shaten, Rockmore and Funk, 1956) compared the effects of chlorpromazine and amobarbital and found that chlorpromazine had no inhibitory effect or facilitated performance on a variety of motor tasks, while amobarbital either had no effect or a deleterious effect on the performance of the same tasks. Since these investigators gave small doses of amobarbital intravenously a comparison of the observed effects of amobarbital with the effects of chronic oral administration of chlorpromazine is difficult to interpret. Lehmann and Hanrahan (Lehmann and Hanrahan, 1954) tested schizophrenic patients on a variety of psychological tests after the administration of chlorpromazine. They found that tapping speed was impaired in 50 per cent. of the subjects. There was no observed impairment on the other tests which were administered.

The findings of facilitation in performance on some tests and very little or no impairment in functioning on others, after chlorpromazine administration in schizophrenics, are contrary to the results of the present study. This suggests either that chronic chlorpromazine administration produces different effects than acute administration or that normal subjects react differently from schizophrenics after chlorpromazine. Further experimentation is at present under way to elucidate this point.

The observations on duration of sleep between 4 and 21 hours following drug administration showed that chlorpromazine caused a significantly greater period of sleep than secobarbital. The duration of sleep following secobarbital did not differ significantly from that following the placebo. This indicates that within four hours of drug administration the hypnotic effects of secobarbital were not apparent under the conditions of this experiment.

The mean partial correlations between the various experimental treatments (drugs and placebos) support the hypothesis that certain factors intrinsic to the individual subjects make them more or less sensitive to drugs of this type. The nature of these factors has not been elucidated; however, there is some evidence (Kornetsky and Humphries, 1957) suggesting that personality plays a role in drug responsivity. This does not imply that there cannot be a subject



X drug interaction, for there obviously is such an interaction. However, there is still a significant tendency for some subjects to show a greater effect than others no matter what drug they are given.

Although the mean effect produced by placebos (compared to the control) was not significant, there was a relationship between placebo scores and drug scores. This suggests that those subjects who were most affected by the placebos were also most affected by the drugs. This agrees with previous studies (Lasagna *et al.*, 1954) which demonstrated that placebo responders also obtained the greatest relief from pain after analgesics.

#### SUMMARY AND CONCLUSIONS

Twelve normal volunteers were given 100 and 200 mg. of chlorpromazine and 100 and 200 mg. of secobarbital on separate days. All drugs were administered orally and the "double-blind" technique was employed throughout. Ninety minutes after the ingestion of the drug, subjects were tested on a variety of psychological tests, and 210 minutes after the drug, blood pressure, pulse, respiration and oral temperature were recorded.

The following conclusions were drawn from the data:

1. At doses of 100 and 200 mg. chlorpromazine has a greater effect on tests of motor co-ordination than 100 and 200 mg. of secobarbital, respectively.
2. Two hundred mg. of secobarbital has a greater effect on a test that is related to intellectual functioning than 200 mg. of chlorpromazine.
3. Four hours after oral ingestion of chlorpromazine and secobarbital, sleep time is significantly increased for both 100 and 200 mg. of chlorpromazine, but not for secobarbital.
4. This study supports a thesis of general drug sensitivity in human subjects. Subjects most affected by one drug are most affected by other drugs.

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# TRENDS IN THE DEVELOPMENT OF PHYSIOLOGY OF THE BRAIN\*

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## INTRODUCTION

THERE is hardly any field of natural science where development is so erratic as that of the physiology of the brain. It is true that perhaps no branch of science develops quite evenly. Very often the domination of old and deeply-rooted theories is so strong that they cannot easily be removed under the pressure of new facts, and consequently they may hamper the progress of science in the given field for many years. But generally the development of natural science is straightforward in the sense that its every stage is a logical consequence of the previous stages, and that particular lines of investigation tend to complement each other and eventually to merge into a single whole.

Unfortunately nothing of this kind is seen at present in the field of the physiology of the brain. This vast and extensive province of neurophysiology, the primary importance of which lies in the fact that the brain "governs" the behaviour of an animal as a whole, has presented up to now a huge assembly of mutually unrelated groups of data, and an aggregation of independent and often contradictory theories. While in other fields of science all specialists use the same language and therefore can always understand each other, the physiology of the brain reminds us of the biblical tower of Babel whose architects had their tongues "confused" and one and the same word took on quite different meanings.

This situation is explained by a number of factors, of which two, perhaps the most important, will be dealt with first as being of a most general and essential character.

First, however, it should be noticed that in every field of science there emerges in the course of progress a definite model of the phenomena concerned, a model enabling its students to systematize the facts they discover, to interpret them, and to set the course of further work. With the progress of research, the model itself, of course, changes quite considerably: it becomes enriched by new details, or is modified, or complicated, or in some rare instances, it is completely abolished and supplanted by a new one. But in the absence of such a model the given branch of science fails to develop into an organized scientific system and remains merely a store of accidental unrelated observations forming no integrated entity.

To give some examples. The model which guided the development of chemistry in the nineteenth and the beginning of the twentieth centuries was the atomic theory supplemented by the theory of valencies, now deepened and enriched by the concepts of atomic structure. The model in modern genetics is the concept of genes. In the physiology of blood circulation, a model has been

\* The subject of a lecture delivered in Cambridge on 12 November 1957.

supplied by Harvey's discovery of the "motions of the heart", enriched later by the mechanics of capillaries and in recent years by demonstration of arteriovenous connections. In the physiology of the spinal cord a model has been afforded by the concept of the reflex arc, more recently deepened and generalized by the principles of neuron organization (see below).

The first factor responsible for the inadequate development of the physiology of the brain is that physiologists have failed to produce a satisfactory and generally accepted model of the function of this organ. When Pavlov, investigating the physiology of higher nervous activity, established the concept of the conditioned reflex, it might have appeared that a road leading toward systematic and orderly study of cerebral functions had been opened. It seemed that, in the same way that the concept of the spinal reflex had become a guiding principle in research on lower functions of the nervous system, so would the conditioned reflex become with regard to the higher functions. Indeed, the first years of research in this field, guided by the idea of the conditioned reflex, proved to be remarkably fertile. But then disappointment followed. First of all, Pavlov himself did not adhere to the idea with absolute faith. The reason was undoubtedly the fact that the behaviour of animals and man, as can be seen in everyday life and even in the most simplified experimental conditions, is so complicated that its conditioned-reflex composition is by no means so evident as is the unconditioned-reflex composition of spinal activity. Pavlov, therefore, was compelled to extend the concept of the conditioned reflex so much that it became tantamount to the concept of association, well known in psychology. Then, by introducing the concepts of irradiation and concentration of excitation and inhibition and their mutual induction (with which we shall deal later on) Pavlov receded even further from his original conception, as he accepted the existence of cortical processes overtly distinct from those of conditioned reflexes. The conditioned reflex concept also came up against criticisms from numerous scientists outside the Pavlovian school: some queried whether conditioned reflexes are really *elementary* phenomena of cortical activity, while others doubted whether the *entire* cortical activity could be thereby elucidated.

Be that as it may, it must be realized that the brain of the higher animals, and especially the cerebral cortex, is for us at present, as far as its activity is concerned, the most mysterious and incomprehensible of all organs of the body. How very limited, fragmentary, and even possibly erroneous, is our knowledge about it is best recognized by those who are directly concerned with its study. This was perfectly understood and felt by Pavlov himself when he wrote the significant words: "In this realm of science, the mountain of the unknown will for a long time tower above the tiny fragments of the known."

The second important factor is that the functioning of the brain is connected in some way with psychological phenomena, known to each of us from introspection and being the subject of a discipline far older than physiology, namely of psychology. Since the behaviour of animals and man can be considered as a manifestation of cerebral processes as well as psychological phenomena it is clear that much the same territory is explored both by physiologists and by psychologists. This fact not only does not help in the exploration of this territory, but on the contrary creates even greater confusion, since both groups of scientists are to some extent antagonistic to each other; and many psychologists believe either that physiology is not competent at all to deal with animal behaviour, or else that it is not yet sufficiently "grown up" to engage in such studies.



On the other hand, psychologists themselves are very much in conflict about the scope and purpose of their research and the evaluation of the phenomena with which they deal. The fact that there are so many names denoting one and the same subject of investigation (zoopsychology, behaviourism, physiological psychology, ethology, neuropsychology, etc.) shows how great a confusion reigns at present among various psychological schools, and that even the psychologists themselves have not found a uniform language.

Lastly, we must remember that on the other side of the territory held by the physiology of higher nervous activity there extends a vast field of research explored by electro-physiological methods, and again between these two fields of investigation there is no close relation.

When all these factors are taken into account one can understand to what extent the physiology of the brain represents nowadays an incoherent tangle of disconnected threads and how particular scientific centres not only fail to support one another but remain in relative isolation or antagonism and frequently have no means of communication at all.

This paper is intended to give a brief description of various trends of the cerebral physiology and to comment on the prospects of further progress, and on the possibilities of rescuing this branch of science from its present state of confusion.

#### THE ORIGIN OF THE PHYSIOLOGY OF THE BRAIN

It seems that in any branch of science there is a decisive point which marks the beginning of its true development, i.e. a point at which the results of research cease to represent unrelated observations and begin to take the shape of an entity susceptible to interpretation, when students cease to be the "forerunners" (usually discovered *a posteriori*) and become regular architects of science in the field concerned. If this is agreed, then we must pick on the seventies of the past century as the turning point in the physiology of the brain. In those years, Hitzig and Fritsch demonstrated that electric stimulation of definite areas of a dog's cortex elicits movements of contralateral extremities, while destruction of the areas gives rise to temporary disturbances in corresponding motor functions. From that time onwards, in almost all countries, but especially in Germany and England, various fields of the cortex were intensively explored with the aid of two methods: stimulation of various points of the exposed cortex in an anaesthetized animal, and testing of the results of ablation of particular areas after the animal has awakened from anaesthesia. The investigations were so numerous and rich in results that by the turn of the century, the chart of the function of the cortex of animals (rabbits, cats, dogs, monkeys and apes) was essentially completed, and, what is more surprising, it has proved to be not very different from that worked out more recently with the aid of infinitely more perfect methods. The investigations demonstrated that the cortex comprises the so-called projective areas representing a cortical counterpart of particular receptor surfaces, the motor area, involved in voluntary movements of particular parts of the body, and areas of undefined function, which expand with the phylogenetic development of the brain and which were most frequently referred to as associative areas. As a rule, the results of the investigations were in conformity with the results of respective histological studies.

However, it is interesting to note that after this general scientific assault, when all the positions susceptible to conquest with the aid of the methods then available had been tackled, development along this line suddenly came to an

end. It seemed that after the functional topography of the cerebral cortex had been mapped out, there was nothing more left to be done in the physiology of the brain.

### THE FOUNDATIONS OF PAVLOV'S RESEARCH

At that time, i.e. at the beginning of the twentieth century, there appeared, however, another essential trend in research on the functioning of the brain, a trend which was but slightly related to that previously referred to and started from different points of departure. The man who initiated it was Pavlov, who termed this field of science the physiology of higher nervous activity.

Pavlov's idea, which guided him throughout more than thirty years of work in this field, may be outlined thus:

1. The entire complex behaviour of the animal observed in its ordinary life is effectuated by the intermediary of the brain (especially of the cerebral cortex, as indicated earlier by Goltz's experiments with decorticated dogs). In other words, the brain represents the apparatus controlling this behaviour much in the same way as the spinal cord constitutes the apparatus controlling spinal reflexes. Consequently, just as by studying spinal reflexes we can learn about the functional mechanisms of the spinal cord, so understanding of the mechanism of the activity of the cerebral cortex may bring an analysis of the complex behaviour of the intact animal.

2. It follows that the behaviour of an animal is, like all other functions of the body, the subject of physiology. Psychological interpretations of animal behaviour are not only unnecessary but even misleading, since they cannot be tested experimentally and are speculative in character.

3. In undertaking the analysis of the complex behaviour of animals, we must first of all find out the elementary phenomena from which it is built up. Such an elementary phenomenon of behaviour is, according to Pavlov, a conditioned reflex, i.e. a reflex which has been acquired by the animal as a result of its individual experience. It is formed when an indifferent stimulus is followed by a stimulus eliciting an inborn (unconditioned) reflex, and consists in the indifferent stimulus acquiring the faculty of eliciting the same response as the inborn.

4. The "true" physiology of the brain is not so much concerned with the study of the effects of stimulation of the brain in anaesthetized animals—since such do not afford a picture of the normal functions of the organ—but rather with investigations involving conditioned reflexes in waking animals. The method of cortical ablation is by no means dropped, but its proper value will become apparent only when results of cerebral lesions are examined not with reference to superficial observation of the general behaviour of the animal, but with reference to their effect on definite conditioned reflexes.

### DEVELOPMENT OF THE PHYSIOLOGY OF HIGHER NERVOUS ACTIVITY

Until the end of Pavlov's life the research work of his school followed almost exclusively the programme outlined above, and it can be divided (of course, rather schematically) into several stages.

*Stage I.* The first fifteen years were mainly devoted to studies on the fundamental properties of conditioned reflexes. In this stage, the foundations of our knowledge of conditioned reflexes were laid, foundations which have been changed but little to this day. First, the conditions of the formation of conditioned reflexes were studied in great detail. It was found that after a

conditioned reflex to a certain stimulus has been formed, the same response is elicited also by similar stimuli (generalization). It was established that extraneous stimuli, applied simultaneously with conditioned stimuli, have an inhibitory effect on conditioned responses (external inhibition). It was shown that the disappearance of a conditioned reflex, which occurs when the conditioned stimulus ceases to "signal" the unconditional stimulus, involves the process of inhibition: i.e. that the conditioned reflex in such instances is not merely abolished, but is antagonized by a newly set up inhibitory reflex (internal inhibition). Various forms of this inhibition were subjected to detailed examination. Thus, the first stage closed with the establishment of the fact that alongside the excitatory conditioned reflexes there exist also inhibitory conditioned reflexes, which restrict and adjust the functioning of the former according to circumstances.

*Stage II.* During the next ten years studies on the dynamics of cortical processes predominated. While the preceding stage in the physiology of higher nervous activity was in character somewhat reminiscent of behaviourism, as it was chiefly devoted to discovering and systematizing the outward properties of conditioned reflexes, the main activity of the second stage was to determine the cortical processes underlying conditioned responses. Pavlov's physiological theory of these processes was based on the extensive and manifold experimentation of his followers on the mutual interrelations of excitatory and inhibitory conditioned reflexes when elicited in various combinations and temporal sequences. These experiments led Pavlov to the following conclusions concerning the dynamics of the cortical processes. He considered, first, that excitatory and inhibitory conditioned stimuli elicit the processes of excitation or inhibition, respectively, at the "point" of their impact in the cerebral cortex. Secondly, these processes, besides being conveyed to the further links of the conditioned-reflex arc, spread, or irradiate, over the given projective area, or even over the whole cortex; and then recede, or concentrate, back to the points of their departure. Thirdly, such expanding or shrinking foci of excitation and inhibition evoke on their periphery processes of opposite sign, which restrict their expansion (positive and negative induction). Thus, cortical function would represent a peculiar, continuously changing interplay of processes of excitation and inhibition arising every moment in various parts of the cortex, spreading and restricting each other according to the constantly changing stimuli from external environment.

It should be borne in mind that the picture of cortical dynamics, outlined here in a very abridged form, represents a certain theory (or rather a working hypothesis), deduced from experimental facts but by no means identical with them. Whether this theory is true or false depends on its congruity both with the whole body of experimental facts upon which it is based and with the general principles of nervous activity. However, owing to the strong faith placed in its correctness, the theory was accepted in Pavlov's school more and more as a dogma, and its statements were considered rather as experimentally proven facts, than as hypotheses necessitating further analysis.

*Stage III.* Finally, in the third stage of the research, Pavlov's attention was concentrated chiefly on phenomena of the functional pathology of cortical activity, and on closely related problems of typology. This vast field of investigation was opened up by the very important discovery that some combinations of excitatory and inhibitory conditioned stimuli may lead to nervous "conflicts" conducive to more or less persistent and pronounced dis-



turbances in conditioned-reflex functions (so-called experimental neuroses). This provided a basis for an experimental pathology of the brain and for a detailed study of the aetiology, symptomatology and therapy of functional nervous disorders. The fact that the intensity and character of experimental neuroses depend largely on the individual characteristics of the animal prompted Pavlov to devote his attention to the typology, and led him to the establishment of his own classification of types of nervous system.

#### PAVLOV'S THEORY AND CONTEMPORARY NEUROPHYSIOLOGY

Here an interesting problem confronts us. Why has the physiology of higher nervous activity failed to win general recognition as a new and important branch of neuro-physiology in spite of the fact that it is based on perfectly sound and rational premises? Why was it that during Pavlov's lifetime research in this field was confined almost exclusively to his own laboratories, and that after his death the genuine Pavlovian line of research (not the applications of his theory to other fields) largely subsided, as if the subject had been exhausted and nothing was left to be done in this field? Why has the vast amount of work carried out by Pavlov's school in the course of some thirty years failed almost completely to elicit any response among physiologists? Is it because Pavlov's aim of physiological interpretation of the mechanisms of animal behaviour is in itself unattainable, or even fantastic, as some would like to think; or is it because neurophysiology is "not yet ripe" to tackle the problem, as others claim?

Some Soviet scientists and their imitators attempted to explain this state of affairs by way of ideological reasons, that is, by the reluctance of the West to acknowledge either the "materialistic" teachings of Pavlov or his authority. Nothing could be more misleading than such an explanation. Everyone who is even slightly familiar with world literature on this subject knows how great is Pavlov's authority among scientists to this day, to what extent the Western "war on Pavlovism" is but a myth, and how profoundly contemporary physiology of the brain is imbued with materialistic tendencies. Let us add that the development of American experimental psychology (behaviourism) was, and still is, greatly influenced by Pavlov's work, and that such terms as "conditioning", "reinforcement", and a host of others, have become its basic concepts. It may even be said that further experimental progress along Pavlov's line, though based on somewhat different principles and conducted by means of slightly modified methods, has been taken over by American psychologists, and their line of research is often referred to as "neo-Pavlovian".

In a monograph entitled "Conditioned Reflexes and Neuron Organization" I tried to make a thorough analysis of this situation, and arrived at the following conclusions. The failure of the physiology of higher nervous activity to become an integral part of contemporary neurophysiology is due to the fact that the model of Pavlov's theory of cerebral processes (developed chiefly in the second stage of his research work) was not congruent with the general model of nervous processes which was evolved from the evidence of numerous investigations concerning lower parts of the nervous system. This general model may be briefly described as follows. The entire nervous system of the higher animals, the brain included, is a vast net-work of neurons arranged in a definite order and representing the functional units of the system. Every neuron has a single long process or axon, dividing into numerous branches and extending either to executive organs or to other neurons with which it is

connected by contact points, called synapses. Every neuron is a generator of nerve impulses, i.e. of electric disturbances carried along axons; reaching executive organs, they throw them into action, and reaching other neurons, they either excite them, i.e. cause them to generate new sets of impulses, or inhibit them, i.e. suppress the generating of impulses incited by other neurons. The system derives the necessary "energy" from receptors which, when excited by external stimuli, give rise to impulses conducted along afferent fibres to nerve centres. Thus, the nervous system represents a vast system of communication functioning on strictly defined principles.

Now, Pavlov's theory of cerebral processes was put forward independently of this general model (which was not yet then completely formed) and, as can easily be demonstrated, is at variance with it. The Pavlovian idea that cortical activity implies waves of excitation and inhibition spreading over the cerebral cortex and then concentrating at the original starting points, circumscribed by opposite processes on their periphery, cannot be harmonized with the model referred to above, and is unlike anything taking place in other parts of the nervous system. Consequently, Pavlov's theory, making use of terms borrowed from the language of neurophysiology, endows these with such a different meaning, or ascribes to them such specific qualities, that it becomes simply unintelligible to a neurophysiologist. The reason that animal psychology profited so much from the achievements of Pavlov's school is because this science discarded all the physiological concepts of Pavlov and limited itself to absorbing the merely empirical portion of his achievements.

In further sections of the monograph, I tried to demonstrate that it is possible to explain the wealth of factual material accumulated by Pavlov's school on the basis of modern neuron theory; and that the physiology of higher nervous activity, modified accordingly, can become a regular part of neurophysiology, offering possibilities of further development.

### BEHAVIOURISM

At the turn of the twentieth century, independently of Pavlov's research work on conditioned reflexes, there developed in America another important line of investigations of animal behaviour, initiated by a prominent American psychologist, E. L. Thorndike, and generally known as behaviourism. The central idea of behaviourism was that all animal and human behaviour should be studied only empirically and that any reference to what the animal thinks or feels is superfluous.

It is beyond the scope of this paper to deal with this province of science in any detail; we are interested here only in those of its general features which are closely related to our own subject.

1. *The "model" of behaviouristic psychology.* Just as the basic concept in the physiology of higher nervous activity is that of the conditioned reflex, so the basic concept of behaviourism is "habit", i.e. any *acquired*, as opposed to *inborn*, motor activity of the organism. Most behaviourists are little concerned, if at all, with the physiological mechanisms of habits, their interests being primarily in the empirical properties of habit formation such as: the rate at which various habits are acquired and the dependence of that rate on all possible factors; the stimuli by which an animal is guided in dominating complex habits; the retention of habits, etc.

2. *Relation to physiology.* It is significant that Thorndike himself did not eschew the physiological approach to the phenomena he investigated and

some of his physiological conceptions, though now entirely forgotten, were highly ingenious. Some of the later authors took the same position, but others were more or less hostile to the physiological approach. The most prominent representative of the trend opposing physiology was the late Prof. C. L. Hull, the main founder of the formalistic system of animal behaviour. In Hull's system the connecting links between the stimulus and the reaction (in physiology, the nervous centres and their activity) are represented by so-called "symbolical constructs", such as: "strength of habit", "reaction potentials", "effective reaction potential", "drive", etc. The constructs are given no other meaning except that of a link between the factors acting upon an animal, and reactions observed.

However, in recent years, we are witnessing the tendency of behaviouristic psychology to come closer to the physiology of higher nervous activity. This fact is shown, for instance, by the dropping of the term "behaviourism" and substitution of the term "physiological psychology". This turn has been brought about mainly by the following factors:

(a) With the progress of methods applied in behaviouristic psychology it became apparent that, instead of the complicated mazes previously used, it is more promising to use simple methods, in which both the stimulus provoking a response, and the response itself are clearly manifest. This has brought together the concepts of habit and conditioned reflex, and has shown that the physiological approach to the phenomena under consideration is, after all, not so remote.

(b) In recent years there has been a renaissance in the study of the behavioural disorders following various cerebral ablations. It has become increasingly clear that, instead of observing superficially the general or "natural" behaviour of animals, it is much more fruitful to check the disorders by strict and definite behaviouristic tests. A pioneer of this line of research was Franz, at the beginning of this century, who was followed by Lashley, Kalisher and many others. So the co-operation between physiologists, and behaviouristic psychologists has become increasingly closer and has involved an exchange of ideas and the eradication of old prejudices.

(c) Finally, according to my own view, pure formalistic behaviourism is in the long run sterile. In fact, if we take the decision to refuse to accept psychological interpretations of animal behaviour, we are bound sooner or later to substitute physiological ones, otherwise we are doomed to remain on a purely empirical level without any possibility of creating a causal system of the facts observed. Therefore I consider that the gradual "physiologization" of behaviouristic psychology is an "historical necessity", and we are now witnessing the acceleration of this very process.

#### "ANALYTICAL" PHYSIOLOGY OF THE BRAIN

It is now time to return to the trend of development referred to at the beginning of our discussion, and to consider what we may call "analytical physiology", namely that which consists of studying the effects of direct stimulation on the exposed brain of anaesthetized animals. It is obvious that as long as electrical stimulation of various points of the cortex was almost the only method available, the scope of the investigations could only be very limited. In fact, it was exhausted when the topography of the motor areas of the cortex of various species of animals had been determined (Ferrier, Sherrington, and others) and when, by applying electrical stimuli varying in



intensity, frequency and sequence, the excitability of this organ has been explored (Heidenheim, Graham Brown).

However, the situation has changed completely with the introduction of electronic amplifiers and sensitive oscillographs which make it possible to examine in detail the electrical activity of the cells of the brain. Forerunners in investigations of this kind, who used simply sensitive galvanometers, can be found as early as the nineteenth century, among them the eminent Polish physiologists Beck and Cybulski. However, genuine and systematic progress in the field began about 1930 with the work of Adrian, who succeeded in recording action potentials of the cortex of anaesthetized animals produced by stimulation of tactile receptors.

The principal idea of the method in question is very simple. "Natural" stimulation of various receptors, or electrical stimulation of definite parts of the nervous system, generate nerve impulses which are conveyed along the nerve fibres and can be registered wherever the "electrical signals" from the site of stimulation reach. This affords a relatively easy means of learning what is connected with what in the nervous system, i.e. we may learn better than previously the functional structure of the system.

This method, usually referred to as neuronography, is applied on a vast scale in neurophysiology, especially in studies of the brain, and is now in use in almost all laboratories concerned. It has made it possible to learn about the interrelations between various parts of the nervous system in such intimate detail as was not to be thought of even a few years ago. The leap thus made in our knowledge of the functional structure of the brain is comparable to that produced in morphology by the advent of the microscope. A further step forward (which may be likened, in a way, to the application of the electron microscope) resulted from the use of microelectrodes and from the recording of action potentials from single nerve cells.

In what relation stand all these investigations, so vastly extending our knowledge of the structure of the nervous system, to the physiology of higher nervous activity? I would cite here a comparison I used elsewhere: "Imagine that our task is to discover what is going on in a certain huge and complicated secret factory without being provided with clues. On the one hand, we could do it by examining both the raw material supplied to the factory and the products delivered from it. If we were allowed to do this, we might change the raw material in order to see what changes there would be in the products, or even destroy some parts of the plant in order to see how that would affect production. From all this evidence we could form some idea how this factory works. Of course these conclusions would be only hypothetical, and must change according to our further knowledge of the factory. But, at the same time, in this way we could have a fair picture of what this factory was intended for. On the other hand, we could find a way into the factory and watch the machinery at work. This, one would imagine, would bring us nearer to a comprehension of functioning of the plant, but as there would be no guide to explain to us the logic and sequence of the processes of production it might happen that we should be at a loss—seeing all the details but unable to understand the whole." (*Brit. Med. J.*, 1949, ii, 944.)

While the divergence in the pathways of development of behaviourism and physiology of higher nervous activity was due rather to the different *approach* and tradition of the students engaged in the respective fields than to the difference of the fields under the exploration, the divergence between the physiology of higher nervous activity and the analytical physiology of the

brain is, as can be seen from the above analogy, of quite another character. Here we are in fact unable to form a junction between the two lines of research, since we cannot understand what is the real functional significance of the interneural connections manifested in such detail by the neuronographical study. For example: what is the functional meaning of the supplementary projective areas in the cortex, of the various suppressing cortical areas, of the complicated connections between cerebral and cerebellar cortex found in such abundance in recent years? There is no possibility yet of giving any reasonable answers to these and many other questions, and all our guesses about them are both unfounded and incapable of being tested.

It seems to me that there are at present only a few ways of bridging the gap between these two lines of investigation. The best and most widely used consists in limited destruction of various areas of the brain or their connections, according to our neuronographic knowledge, and in studying the effect of this destruction upon various activities of the animal. With this method of investigation there is a good possibility of co-operation, as mentioned above, between neurophysiology and behaviouristic psychology. However, even more desirable in my view, would be a close liaison between the "analytical" approach, as represented by neuronography, and the "synthetic" approach, as represented by the physiology of higher nervous activity. For, although psychological tests can give us exact evidence of what is wrong in a particular sphere of behaviour after a particular cerebral lesion, they cannot supply us with the proper physiological explanation of the observed disorders. This can be done, by definition, only by the physiology of higher nervous activity. Therefore I am convinced that, without swift progress in this field, a progress which should supply us with a general framework, even though inexact and incomplete, of the normal activity of the cerebral cortex, our proper evaluation of the results of particular lesions and consequently our understanding of the functional significance of respective cerebral areas will be impossible.

#### SUMMARY AND CONCLUSIONS

From the foregoing analysis of the main trends in the development of the physiology of the brain and the connections and divergencies between these trends, one can discern, I think, the perspectives of further progress in this field.

To clarify the picture we might summarize the trends and indicate their mutual relations.

1. "Analytical" physiology of the brain, initiated by the Hitzig and Fritsch experiments concerning the electrical stimulation of the motor cortex, and recently expanded into a vast province of science through the methods of modern neuronography.
2. Physiology of higher nervous activity, founded and developed by Pavlov and his school, and concerned with the study of the central mechanisms governing acquired animal behaviour.
3. Behaviouristic psychology, initiated by Thorndike, the aim of which was to investigate acquired behaviour "as such", without reference either to psychological phenomena or to nervous processes.

When Pavlov, having laid the foundation of the physiology of higher nervous activity in the first ten years of research in this field, engaged in establishing a theory of cortical processes, the general laws of the functioning of the central nervous system were still largely unknown. Not finding a suitable basis for his research in the neurophysiology of that time, Pavlov went his own way, and created a quite independent system of ideas and hypotheses which, he believed, was adequate to explain the experimental facts rapidly accumulating in his laboratories. Thus a theory of cortical processes was established based on principles different from those which guided the research work concerned with other parts of the nervous system and carried out in other laboratories. It should be added that Pavlov frequently made it clear that he himself did not consider his theory as a dogma non-susceptible of further discussion. On the contrary, he saw its weak points and not infrequently modified it quite drastically. However, he failed to substitute for it a new compact system that would adequately account for the vast wealth of facts gathered by his school.

For these reasons, Pavlov's theory of cortical processes could not play the part of a framework in the physiology of the brain, as did Sherrington's concepts—developed at about the same time—as regards the functioning of the spinal cord; thus, the physiology of higher nervous activity failed to become “assimilated” by neurophysiology as an important new branch. This involved two important consequences. On the one hand, the behaviourists, though representing a trend quite close to that of the physiology of higher nervous activity by which they were greatly influenced, declined to assimilate Pavlov's theory of cortical processes (even in spite of their not infrequent good will), and turned away altogether from the physiological approach to the problems of behaviour, going the way of formalism. On the other hand, contemporary neurophysiology became mainly “analytical” in character, dealing primarily with the architecture of the connections between particular parts of the brain, and caring but little for their functional significance.

It is obvious that this abnormal situation could not continue indefinitely. Analytical physiology being increasingly successful, its students were bound to strive to understand the functional significance of the connections they detected. As a result they have been forced to call upon the assistance of either the behaviourist, or the physiologist of higher nervous activity. This has led to a lessening in the formalistic tendency of behaviouristic psychology, which manifests itself in the term “physiological psychology”. Neuro-physiologists, on the other hand, realize with increasing clarity that effective help may be forthcoming chiefly from the physiology of higher nervous activity, for the latter operates with phenomena whose physiological mechanism is more or less intelligible.

Therefore it seems to me that we are now approaching a very important era in the development of the physiology of the brain: Pavlovian physiology of the higher nervous activity, behaviouristic or physiological psychology, and analytical neuro-physiology of the brain, till now rather separate and even antagonistic, are beginning to merge and their respective students are beginning to understand each other. The study of the cerebral functions will no doubt continue to be the most difficult and the least accessible branch of physiology, but there are grounds for hoping that the factors obstructing its progress will eventually be removed.



# THE DIAGNOSTIC AND PREDICTIVE ACCURACY OF THE WECHSLER MEMORY SCALE IN PSYCHIATRIC PATIENTS OVER 65

By

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IN a previous study of the efficacy of a vitamin-preparation (Krawiecki, Couper and Walton, 1957), the Wechsler Memory Scale Form I (1945) was administered on four occasions to each senile psychotic patient in the trial. Although the experiment produced interesting therapeutic results the present paper is not concerned with these but rather with the diagnostic and predictive implications of the Memory Scale changes.

At the beginning of the experiment all the cases clinically manifested a memory defect, presumed to be associated with cerebral changes. At the end of the experiment some of the control group, treated with an inactive preparation, had shown very significant rises in their scores on the Memory Scale. Since some of these had been very large it suggested that these patients might not have been brain-damaged or were less so than those patients who had shown little or no change on successive re-testings. It further suggested that the size of these changes resulting from the administration of the Memory Scale on four occasions, might be of greater diagnostic value than the results from a single testing. The effects of long periods of hospitalization and consequent lack of mental stimulation might easily have produced an "apparent" memory disorder with a resulting diagnosis of dementia. If the patient was given the opportunity to learn through successive repetitions however, it might show that the memory disorder was reversible and the diagnosis of dementia less certain.

It was therefore considered necessary to follow up the original group of cases for a further period of two years to be more certain of the diagnoses and then to relate these to the memory scale changes. In this way the diagnostic and predictive accuracy of the Memory Scale with regard to the problem of senile dementia could be more accurately evaluated.

## METHOD

A period of two years elapsed before the records of the 50 patients were again examined. The 1955 diagnosis was then compared with the changes in symptomatology to discover, for example, whether the patient had recovered and had been discharged, whether there had been an intensification of the previous organic picture, whether regrading to voluntary status had taken place because of improvement and whether the patient was considered to have suffered previously from an affective rather than organic condition. During the period covered by the examination of the case records no reference was made to the Memory Scale changes.

As one half of the patients had previously received Parentrovite and the

other half a placebo, the two groups were examined separately to avoid a possible contamination in the results. Full information on the experimental group was obtained although data was available on only 23 of the control group.

### RESULTS

Tables I and II show the two diagnoses for each patient in 1955 and 1957, the first Wechsler Memory Quotient (1955), the changes between this and the fourth Memory Scale Assessment, and relevant follow-up comments.

The significance of the experimental and control group changes was then evaluated. The two groups were again treated separately.

### DISCUSSION

It is apparent from Tables I and II that the size of the Memory Scale changes bears a relationship to the final diagnosis (1957). Both sets of results suggest that the size of the changes between the first and final assessments was of greater predictive validity than the diagnosis in 1955. Detailed examination of these tables shows that of the eleven changes in diagnosis for the experimental group and the seven in the control group, larger increases between the 1st and 4th assessments were obtained by those patients subsequently diagnosed as affective or discharged from hospital as recovered, in contrast to those who made much smaller increases and who either had the diagnosis of organicity confirmed or whose diagnosis changed from an affective disorder to one of dementia.

A more precise statistical treatment of these changes is contained in Table III and IV. The organics and functionals (1957 diagnosis) in both the experimental and control groups were closely equated for age (Tables III (*d*), IV (*d*)). Although the mean M.Q.s of the organics and functionals (1955 diagnosis) in the experimental group showed a statistically significant difference, there was a considerable overlap between these groups. The level of confidence was only between the .05 and .02 levels (Table III (*a*)). Since, however, the majority of these patients had been hospitalized for many years, it was not inconceivable that some of the patients diagnosed as suffering from dementia were in fact suffering from a pseudo-dementia. It was decided therefore to compare the 1957 diagnosis with the 4th M.Q. results. The result shows a very high level of statistical significance (Tables III (*b*, *c*)). The significant reduction in the number of misclassifications can be seen by reference to Table VA. If the cut-off point was first established at M.Q. 91, then all the 1955 organics scored less than this, though 60 per cent. of the 1955 affective group did the same. In contrast, if the 4th M.Q. and the 1957 diagnosis were taken, the cut-off point could be lowered to a M.Q. of 81. This would correctly identify 14 of the 16 organics, with no misclassification in the affective group. Similar results to these were obtained in the control group. Using the 1955 diagnosis and the 1st M.Q. a statistically significant difference was found between the organic and functional groups, though again a number of misclassifications occurred (Tables IV (*a*), VB). When the 1957 diagnosis was used with the 4th M.Q. results, a higher level of statistical reliability was achieved. This could not be attributed to a difference in the ages of the two groups, as no significant difference in age was established between the groups (Table IV (*d*)). Table VB shows that if a cut-off point was made at M.Q. 86, all the organics scored less than this and nine of the twelve functionals obtained scores above this point.

The initial diagnoses and the first M.Q. assessments were clearly not very reliable, though the results of the fourth assessment corresponded most closely with the final diagnosis. One of the most important distortions appeared to be the length of hospitalization with its resulting apathy. The importance of intensive stimulation, as presented, for example, by the successive re-testings, obviated this effect in the functionals to a considerable degree. For both the experimental and control groups there were large differences between the first and final M.Q.s for those subsequently considered to be suffering from an affective disturbance or who had been discharged as recovered. Those finally diagnosed as organics made much less progress on successive re-testings. The results from repeated re-testings, based on the principle of successive opportunities to learn, appeared of considerable predictive and diagnostic importance.

In spite of the predictive accuracy of the full scale however, it would be uneconomical to administer it several times when a diagnostic problem of possible senile dementia occurred. A shorter test involving the same principle of successive opportunities to learn appeared necessary. Further refinement could be achieved by analysing those sections of the test which were most impaired in those finally diagnosed as organic. Items which failed to discriminate could be omitted. Of particular relevance to this refinement is the experimental work of Ingham (1952). He suggested that memory could be divided into two sections based on general intelligence and a factor which he called "m" or retentivity: ". . . retained items . . . depend more upon 'm' than upon 'g', whilst both learning and immediate memory scales depend more upon 'g'."

The Memory Scale sub-tests were then examined. They were divided into those considered to be better measures of retentivity or "m", and those heavily dependent on present learning ability. Table VI shows the results from the different methods of analysis. The fourth Memory Scale assessment only was used. Those items referring to the patient's name, date of birth, and recitation of the alphabet were included under retentivity (R). Because the maximum retentivity score was only 5, the raw scores were multiplied by 14.6 to be comparable with the maximum learning score of 73. The learning score (L) comprised the patient's raw scores for meaningful passages, digits forward and back, visual memory and associate learning sub-tests.

Although there are patently large differences between the mean scores of the organics and functionals which need no finer statistical evaluation, detailed examination of the individual "Retentivity" and "Learning" items shows that only the "Learning" scores are of diagnostic value. In the experimental group, for example, the lowest retentivity score for the non-organics was 43.8. Seven of the sixteen brain-damaged subjects scored higher than or equal to this. In contrast the lowest learning score for the non-brain damaged was 22.0, whilst 13 of the brain-damaged group scored less than this. Similarly, in the non-brain damaged control group, ten patients scored over 40 in retentivity, whilst 3 of the eleven brain-damaged subjects scored more than this. In respect of the learning score, however, of the twelve non-brain damaged patients, eight scored more than thirty, whilst 10 of the 11 brain-damaged subjects scored less than this. The results appear to suggest that in psychiatric patients over 65, particularly those diagnosed as organic, present learning ability, as measured by the patient's ability to improve his performance on the final sub-tests over a period of four trials, is less than their ability to retain previously learned material. Since the functional patients also show this difference, though to a much less a degree, it is expected to be an exaggeration of the normal ageing process. Retentivity also seems affected in the organics, though much less than present learning ability.



TABLE I

*Diagnostic and Memory Scale Changes for the Experimental Group Treated with Parentrovite*

| No. | Age<br>(1955) | Years in<br>Hospital<br>(1955) | Diagnosis<br>(1955)                            | 1st<br>M.Q.<br>(1955) | Diagnosis<br>(1957)     | M.Q.<br>Difference<br>(4th-1st) | Follow-up<br>Comments                                 |
|-----|---------------|--------------------------------|------------------------------------------------|-----------------------|-------------------------|---------------------------------|-------------------------------------------------------|
| 1   | 77            | 1                              | Senile dementia                                | 64                    | Affective Disorder      | +23                             | Discharged,<br>recovered.                             |
| 2   | 77            | 9                              | Senile dementia                                | 83                    | Senile dementia         | -14                             |                                                       |
| 3   | 78            | 42                             | Secondary dementia                             | 50                    | Secondary dementia      | +12.5                           |                                                       |
| 4   | 87            | 30                             | Senile dementia                                | 51                    | Senile dementia         | +5                              |                                                       |
| 5   | 74            | 2                              | Depressive with<br>paranoid features           | 94                    | Senile depressive state | +28.5                           | Died, lung cancer.                                    |
| 6   | 73            | 1                              | Senile dementia                                | 60                    | Senile dementia         | +10                             |                                                       |
| 7   | 75            | 2                              | Presbyophrenia                                 | 63                    | Presbyophrenia          | +19.5                           |                                                       |
| 8   | 75            | 33                             | Delusional insanity                            | 62                    | Senile dementia         | +2                              |                                                       |
| 9   | 71            | 1                              | Senile dementia                                | 69                    | Affective Disorder      | +17                             | Discharged.                                           |
| 10  | 68            | 12                             | Korsakow psychosis                             | 87                    | Korsakow psychosis      | +7                              | Regraded voluntary.                                   |
| 11  | 67            | 32                             | Delusional insanity                            | 61                    | Secondary dementia      | +11                             |                                                       |
| 12  | 65            | 3                              | Anxiety-depression                             | 76                    | Anxiety-depression      | +27                             |                                                       |
| 13  | 69            | 30                             | Secondary dementia                             | 62                    | Senile dementia         | +1                              |                                                       |
| 14  | 65            | 32                             | Delusional insanity<br>Secondary dementia      | 59                    | Delusional insanity     | +25.5                           | Regraded voluntary<br>works well,<br>orientated.      |
| 15  | 67            | 1                              | Senile dementia                                | 90                    | Affective Disorder      | +25.5                           | Discharged after<br>trial, made good<br>recovery.     |
| 16  | 67            | 24                             | Senile dementia                                | 53                    | Senile dementia         | +11                             | Died, cardiovascular<br>degeneration.                 |
| 17  | 70            | 12                             | Delusional insanity                            | 100                   | Delusional insanity     | +14                             |                                                       |
| 18  | 70            | 19                             | Melancholia                                    | 100                   | Secondary dementia      | +10                             |                                                       |
| 19  | 69            | 4                              | Senile dementia                                | 48                    | Senile dementia         | 0                               | Died, peripheral<br>failure, myo-<br>cardiac disease. |
| 20  | 66            | 32                             | Melancholia                                    | 58                    | Senile dementia         | +3                              |                                                       |
| 21  | 72            | 23                             | Senile dementia                                | 59                    | Senile dementia         | +3                              |                                                       |
| 22  | 70            | 32                             | Mania                                          | 62                    | Secondary dementia      | +11                             |                                                       |
| 23  | 70            | 24                             | Delusional insanity with<br>secondary dementia | 49                    | Secondary dementia      | +11                             |                                                       |
| 24  | 65            | 6                              | Manic-depressive<br>psychosis                  | 99                    | Manic depressive        | +9                              |                                                       |
| 25  | 76            | 50                             | Dementia                                       | 48                    | Dementia                | 0                               | Died, cardiovascular<br>degeneration.                 |

TABLE II

*Diagnostic and Memory Scale Changes for the Control Group Treated with Placebo*

| No. | Age<br>(1955) | Years in<br>Hospital<br>(1955) | Diagnosis<br>(1955)                  | 1st<br>M.Q.<br>(1955) | Diagnosis<br>(1957) | M.Q.<br>Difference<br>(4th-1st) | Follow-up<br>Comments                                                    |
|-----|---------------|--------------------------------|--------------------------------------|-----------------------|---------------------|---------------------------------|--------------------------------------------------------------------------|
| 1   | 75            | 46                             | Mania                                | 69                    | Mania               | +32.5                           |                                                                          |
| 2   | 72            | 30                             | Primary dementia                     | 89                    | Primary dementia    | +11                             | De-certified, trans-<br>ferred to old men's<br>home.                     |
| 3   | 77            | 5                              | Senile dementia                      | 62                    | Senile dementia     | 0                               |                                                                          |
| 4   | 65            | 4                              | Anxiety-depressive                   | 87                    | Anxiety-depressive  | +21                             | Died, broncho-<br>pneumonia.                                             |
| 5   | 66            | 5                              | Melancholia                          | 57                    | Senile dementia     | +9                              | Died, cardiovascular                                                     |
| 6   | 65            | 21                             | Delusional insanity                  | 70                    | Delusional insanity | +42                             |                                                                          |
| 7   | 65            | 28                             | Melancholia/dementia                 | 64                    | Senile dementia     | +17                             |                                                                          |
| 8   | 65            | 1                              | Dementia                             | 56                    | Dementia            | +17                             |                                                                          |
| 9   | 65            | 42                             | Melancholia, secondary<br>dementia   | 55                    | Secondary dementia  | +11                             |                                                                          |
| 10  | 79            | 4                              | Senile dementia                      | 48                    | Senile dementia     | +7                              |                                                                          |
| 11  | 79            | 1                              | Senile depression                    | 69                    | Depression          | +10.5                           |                                                                          |
| 12  | 79            | 30                             | Senile dementia                      | 59                    | Senile dementia     | +2                              |                                                                          |
| 13  | 77            | 6                              | Depressive state                     | 60                    | Depressive state    | +16                             | Discharged,<br>recovered.                                                |
| 14  | 83            | 1                              | Melancholia                          | 94                    | Melancholia         | +30                             |                                                                          |
| 15  | 75            | 2                              | Senile dementia                      | 56                    | Senile dementia     | +8                              |                                                                          |
| 16  | 76            | 9                              | Senile dementia                      | 67                    | Senile dementia     | +17                             | Died, cardiovascular<br>degeneration.                                    |
| 17  | 82            | 53                             | Senile dementia                      | 66                    | Affective Disorder  | +24                             | Well orientated,<br>senile weakness.                                     |
| 18  | 78            | 50                             | Secondary dementia                   | 59                    | Secondary dementia  | +21                             | Died, cardiovascular<br>disease.                                         |
| 19  | 72            | 3                              | Melancholia                          | 79                    | Melancholia         | +14                             |                                                                          |
| 20  | 72            | 11                             | Melancholia                          | 66                    | Melancholia         | +4                              | Died, cancer of<br>prostate.                                             |
| 21  | 66            | 32                             | Delusional, secondary<br>dementia    | 73                    | Delusional insanity | +39                             | Re-graded voluntary,<br>orientation good.                                |
| 22  | 73            | 43                             | Melancholia, secondary<br>dementia   | 58                    | Secondary dementia  | -1                              |                                                                          |
| 23  | 71            | 26                             | Delusional insanity<br>with dementia | 74                    | Delusional insanity | +29                             | Re-graded voluntary,<br>bright, cheerful<br>and correctly<br>orientated. |

TABLE III

*Mean Memory Quotients, Significant Differences, Ranges, t Test Results for the Experimental Group Treated with Parentrovite*

|                     | Mean<br>1st M.Q.                    | S.D. | Range      | t Test                |
|---------------------|-------------------------------------|------|------------|-----------------------|
| (a) 1955 Diagnosis: |                                     |      |            |                       |
| Organics ..         | 62.1                                | 13.8 | 48 - 90    | 2.23, significant     |
| Functionals ..      | 77.5                                | 17.4 | 58 - 100   | 0.05-.02              |
|                     | Mean<br>4th M.Q.                    | S.D. | Range      | t Test                |
| (b) 1957 Diagnosis: |                                     |      |            |                       |
| Organics ..         | 67.2                                | 15.3 | 48 - 110   | 5.16, significant     |
| Functionals ..      | 100.3                               | 14.4 | 82.5-122.5 | <.01                  |
|                     | Mean<br>M.Q.<br>Change<br>(4th-1st) | S.D. | Range      | t Test                |
| (c) 1957 Diagnosis: |                                     |      |            |                       |
| Organics ..         | +5.2                                | 6.55 | -14 +12.5  | 5.7, significant      |
| Functionals ..      | +21.0                               | 6.08 | +9 - 28.5  | <.01                  |
|                     | Mean<br>Age                         | S.D. | Range      | t Test                |
| (d) 1957 Diagnosis: |                                     |      |            |                       |
| Organics ..         | 72.1                                | 5.4  | 66 - 87    | 1.12, not significant |
| Functionals ..      | 69.8                                | 4.4  | 65 - 77    |                       |

TABLE IV

*Mean Memory Quotients, Significant Differences, Ranges, t Test Results for the Control Group Treated with Placebo*

|                     | Mean<br>1st M.Q.                    | S.D.  | Range    | t Test                    |
|---------------------|-------------------------------------|-------|----------|---------------------------|
| (a) 1955 Diagnosis: |                                     |       |          |                           |
| Organics ..         | 61.3                                | 7.1   | 48 - 74  | 2.82, significant .02-.01 |
| Functionals ..      | 74.0                                | 11.96 | 57 - 94  |                           |
|                     | Mean<br>4th M.Q.                    | S.D.  | Range    | t Test                    |
| (b) 1957 Diagnosis: |                                     |       |          |                           |
| Organics ..         | 68.0                                | 9.5   | 55 - 84  | 5.28, significant <.01    |
| Functionals ..      | 97.4                                | 15.58 | 70 - 124 |                           |
|                     | Mean<br>M.Q.<br>Change<br>(4th-1st) | S.D.  | Range    | t Test                    |
| (c) 1957 Diagnosis: |                                     |       |          |                           |
| Organics ..         | +9.8                                | 7.2   | -1 - +21 | 3.10, significant         |
| Functionals ..      | +22.7                               | 11.5  | +4 - +42 | <.01                      |
|                     | Mean<br>Age                         | S.D.  | Range    | t Test                    |
| (d) 1957 Diagnosis: |                                     |       |          |                           |
| Organics ..         | 72.5                                | 5.75  | 65 - 79  | .29, not significant      |
| Functionals ..      | 73.2                                | 5.2   | 65 - 83  |                           |





TABLE VI

*Individual and Group Mean Learning (L) and Retentivity (R) Scores for the Experimental and Control Groups, using the 4th Assessment Results and the 1957 Diagnosis*

| Experimental Group |       |          |       | Control Group |       |          |       |
|--------------------|-------|----------|-------|---------------|-------|----------|-------|
| Functionals        |       | Organics |       | Functionals   |       | Organics |       |
| R                  | L     | R        | L     | R             | L     | R        | L     |
| 73.0               | 26.0  | 73.0     | 15.0  | 29.2          | 48.0  | 0        | 0     |
| 73.0               | 57.5  | 29.2     | 9.5   | 58.4          | 17.5  | 14.6     | 25.0  |
| 73.0               | 22.5  | 14.6     | 12.0  | 73.0          | 22.0  | 29.2     | 32.5  |
| 43.8               | 22.0  | 58.4     | 18.0  | 73.0          | 46.5  | 14.6     | 28.0  |
| 73.0               | 34.0  | 73.0     | 15.5  | 73.0          | 28.0  | 14.6     | 23.5  |
| 43.8               | 27.5  | 73.0     | 27.0  | 58.4          | 31.0  | 29.2     | 10.0  |
| 58.4               | 50.5  | 58.4     | 18.0  | 29.2          | 17.5  | 14.6     | 17.0  |
| 58.4               | 43.5  | 43.8     | 14.0  | 43.8          | 41.5  | 58.4     | 21.0  |
| 58.4               | 45.0  | 14.6     | 18.0  | 58.4          | 36.5  | 58.4     | 23.5  |
|                    |       | 73.0     | 47.0  | 73.0          | 36.5  | 58.4     | 5.0   |
| 554.8              | 328.5 | 0        | 0     | 58.4          | 35.0  | 0        | 0     |
|                    |       | 0        | 17.0  | 73.0          | 39.5  |          |       |
|                    |       | 29.2     | 16.0  |               |       | 292.0    | 185.5 |
|                    |       | 14.6     | 25.5  | 700.8         | 399.5 |          |       |
|                    |       | 14.6     | 18.0  |               |       |          |       |
|                    |       | 0        | 0     |               |       |          |       |
|                    |       | 569.4    | 270.5 |               |       |          |       |
| Means:             |       |          |       |               |       |          |       |
| 61.6               | 36.5  | 35.5     | 16.9  | 58.4          | 33.2  | 26.5     | 16.8  |

## CONCLUSIONS

1. Although a single testing with the memory scale resulted in a high percentage of misclassification, repetition of the test apparently produced two different responses in the functional and organic patient. The functional patient improved his performance to a more significant degree than the organic and these differences were of considerable diagnostic and predictive importance.

2. Depression and the apathy induced by lengthy periods of hospitalization can result in an apparently poor memory, which, in psychiatric patients over 65, might easily result in a faulty diagnosis of dementia.

3. Examination of the "retentivity" and "learning" scores on the fourth assessment, for both the organic and functional patients, showed that a relatively inferior learning ability distinguished the organic from the functional patient.

4. In spite of the accuracy of the Memory Scale it is uneconomical to be forced to administer the scale on four occasions. The necessity of developing therefore a test of dementia which was short and which combined both the principle of successive re-testings and which depended for success on present learning ability was indicated.

## SUMMARY

A two-year follow-up study of 50 senile psychotics was carried out to establish more reliably the diagnosis of each case and to compare possible changes in diagnosis with Wechsler Memory Scale scores and changes in these following four repetitions of the test. In this way the validity of the Memory Scale with regard to the diagnosis of senile dementia could be more accurately evaluated.

The results showed that the presence of depression, or the adverse effect of long periods of hospitalization often resulted in an apparent memory disorder reflected both in a spuriously low first Memory Scale performance and a false diagnosis of dementia. After the fourth administration of the Scale, the final score and the extent to which the patient had been able to improve his performance were compared with the final diagnosis and outcome. There was

a close relationship between significant improvement in test performance and a final diagnosis of a functional disorder, compared with the more limited improvement of the organic.

Additional analysis of the results on the Memory Scale sub-tests suggested that those patients subsequently diagnosed as brain-damaged showed most difficulty in learning new material, in contrast to those "functional" patients who showed this disability to a much less degree.

The results strongly suggested that a valid test of dementia should consist of a relatively pure measure of present learning ability, and that this could best be provided by successive repetitions of the test.

#### ACKNOWLEDGMENTS

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# THE DIAGNOSTIC AND PREDICTIVE ACCURACY OF THE MODIFIED WORD LEARNING TEST IN PSYCHIATRIC PATIENTS OVER 65

By

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In a previous paper the results of a two-year follow-up study were reported (Walton, 1958). This study showed that when the Wechsler Memory Scale was administered four times to each patient of a series suffering from a memory defect, significant differences emerged between those patients subsequently diagnosed as brain-damaged or as non-brain-damaged, in respect of the degree of improvement in their performance. The results were of considerable diagnostic and predictive importance. In spite of this, however, the method would be an uneconomical method for routine diagnosis. A shorter test involving the same principle of successive opportunities to learn appeared necessary. Additional analysis of the final Memory Scale results also showed that present learning ability was more impaired in the organic group than in the non-brain-damaged group, whilst scores based on retentivity questions produced many misclassifications. The results strongly suggested that a test of dementia should consist of a measure of present learning ability and that opportunities to learn could best be provided by successive repetitions of the particular test.

A word-learning test developed by Nelson (1953) and Shapiro and Nelson (1955), to test Babcock's theory that a significant discrepancy between past and present learning ability was consistent with dementia, appeared relevant to this problem. The Terman-Merrill vocabulary test was administered until there were five consecutive failures. The subject was required to learn and retain the meanings of these five previously unknown words.

It has always appeared to the author that the New Word Learning Test was too easy to be useful in the detection of brain damage and that its usefulness could be increased by retaining the principles on which the test was developed, while increasing its level of difficulty. The principle of successive opportunities to learn had previously been applied in the use of the Rorschach and Goldstein tests for the detection of brain damage. Since, however, these tests and others were influenced by intelligence, a crucial test of the validity of this principle was not possible (Diers and Brown, 1951; Yates, 1954; Walton, 1955; Shapiro and Nelson, 1955). In the New Word Learning Test, where the patient was required to learn at a level supposedly consistent with his intelligence, this distorting variable was expected to be minimized. Shapiro and Nelson (1955) did find that this was not generally so and were forced to conclude that the ability to learn and retain new words was also dependent in part on level of intelligence. The test failed to differentiate significantly between brain-damaged and non-brain-damaged patients. A study which has just been completed, however, has shown that vocabulary level in normals, as measured by



TABLE I

*Diagnostic and Memory Scale Changes and Learning Test Scores for the Experimental Group Treated with Parentrovite*

| No. | Age<br>(1955) | Years in<br>Hospital<br>(1955) | Diagnosis<br>(1955)                               | Diagnosis<br>(1957)           | M.Q.<br>Differ-<br>ence<br>(4th-1st) | M.W.L.T.<br>Score | Follow-up<br>Comments                                   |
|-----|---------------|--------------------------------|---------------------------------------------------|-------------------------------|--------------------------------------|-------------------|---------------------------------------------------------|
| 1   | 77            | 1                              | Senile dementia                                   | Affective disorder            | +23                                  | 18                | Discharged, recovered.                                  |
| 2   | 77            | 9                              | Senile dementia                                   | Senile dementia               | 14                                   | 33                |                                                         |
| 3   | 78            | 42                             | Secondary dementia                                | Secondary dementia            | +12.5                                | 38                |                                                         |
| 4   | 87            | 30                             | Senile dementia                                   | Senile dementia               | +5                                   | 40+               |                                                         |
| 5   | 74            | 2                              | Depressive with<br>paranoid features              | Senile depressive state       | +28.5                                | 9                 | Died, lung cancer.                                      |
| 6   | 73            | 1                              | Senile dementia                                   | Senile dementia               | +10                                  | 40+               |                                                         |
| 7   | 75            | 2                              | Presbyophrenia                                    | Presbyophrenia                | +19.5                                | 26                |                                                         |
| 8   | 75            | 33                             | Delusional insanity                               | Senile dementia               | +2                                   | 40+               |                                                         |
| 9   | 71            | 1                              | Senile dementia                                   | Affective disorder            | +17                                  | 22                | Discharged.                                             |
| 10  | 68            | 12                             | Korsakow psychosis                                | Korsakow psychosis            | +7                                   | 30                | Re-graded voluntary.                                    |
| 11  | 67            | 32                             | Delusional insanity                               | Secondary dementia            | +11                                  | 25                |                                                         |
| 12  | 65            | 3                              | Anxiety depression                                | Anxiety depression            | +27                                  | 8                 |                                                         |
| 13  | 69            | 30                             | Secondary dementia                                | Senile dementia               | +1                                   | 40+               |                                                         |
| 14  | 65            | 32                             | Delusional insanity<br>secondary dementia         | Delusional insanity           | +25.5                                | 14                | Re-graded voluntary,<br>works well, orien-<br>tated.    |
| 15  | 67            | 1                              | Senile dementia                                   | Affective disorder            | +25.5                                | 9                 | Discharged after trial,<br>made good recovery.          |
| 16  | 67            | 24                             | Senile dementia                                   | Senile dementia               | +11                                  | 40+               | Died, cardiovascular<br>degeneration.                   |
| 17  | 70            | 12                             | Delusional insanity                               | Delusional insanity           | +14                                  | 3                 |                                                         |
| 18  | 70            | 19                             | Melancholia                                       | Secondary dementia            | +10                                  | 2                 |                                                         |
| 19  | 69            | 4                              | Senile dementia                                   | Senile dementia               | 0                                    | 40+               | Died, peripheral fail-<br>ure, myocardiac dis-<br>ease. |
| 20  | 66            | 32                             | Melancholia                                       | Senile dementia               | +3                                   | 40+               |                                                         |
| 21  | 72            | 23                             | Senile dementia                                   | Senile dementia               | +3                                   | 5                 |                                                         |
| 22  | 70            | 32                             | Mania                                             | Secondary dementia            | +11                                  | 38                |                                                         |
| 23  | 70            | 24                             | Delusional insanity<br>with secondary<br>dementia | Secondary dementia            | +11                                  | 35                |                                                         |
| 24  | 65            | 6                              | Manic-depressive<br>psychosis                     | Manic-depressive<br>psychosis | +9                                   | 5                 |                                                         |
| 25  | 76            | 50                             | Dementia                                          | Dementia                      | 0                                    | 40+               | Died, cardiovascular<br>degeneration.                   |

TABLE II

*Diagnostic and Memory Scale Changes and Learning Test Scores for the Control Group Treated with Placebo*

| No. | Age<br>(1955) | Years in<br>Hospital<br>(1955) | Diagnosis<br>(1955)                  | Diagnosis<br>(1957) | M.Q.<br>Differ-<br>ence<br>(4th-1st) | M.W.L.T.<br>Score | Follow-up<br>Comments                                                 |
|-----|---------------|--------------------------------|--------------------------------------|---------------------|--------------------------------------|-------------------|-----------------------------------------------------------------------|
| 1   | 75            | 46                             | Mania                                | Mania               | +32.5                                | 12                |                                                                       |
| 2   | 72            | 30                             | Primary dementia                     | Primary dementia    | +11                                  | 12                | Decertified, transferred<br>to old men's home.                        |
| 3   | 77            | 5                              | Senile dementia                      | Senile dementia     | 0                                    | 40+               |                                                                       |
| 4   | 65            | 4                              | Anxiety depressive                   | Anxiety depressive  | +21                                  | 13                | Died, broncho-<br>pneumonia.                                          |
| 5   | 66            | 5                              | Melancholia                          | Senile dementia     | +9                                   | 40+               | Died, cardiovascular<br>disease.                                      |
| 6   | 65            | 21                             | Delusional insanity                  | Delusional insanity | +42                                  | 7                 |                                                                       |
| 7   | 65            | 28                             | Melancholia/dementia                 | Senile dementia     | +17                                  | 38                |                                                                       |
| 8   | 65            | 1                              | Dementia                             | Dementia            | +17                                  | 40+               |                                                                       |
| 9   | 65            | 42                             | Melancholia, secondary<br>dementia   | Secondary dementia  | +11                                  | 40+               |                                                                       |
| 10  | 79            | 4                              | Senile dementia                      | Senile dementia     | +7                                   | 40+               |                                                                       |
| 11  | 79            | 1                              | Senile depression                    | Depression          | +10.5                                | 16                |                                                                       |
| 12  | 79            | 30                             | Senile dementia                      | Senile dementia     | +2                                   | 40+               |                                                                       |
| 13  | 77            | 6                              | Depressive state                     | Depressive state    | +16                                  | 7                 | Discharged, recovered.                                                |
| 14  | 83            | 1                              | Melancholia                          | Melancholia         | +30                                  | 8                 |                                                                       |
| 15  | 75            | 2                              | Senile dementia                      | Senile dementia     | +8                                   | 40+               |                                                                       |
| 16  | 76            | 9                              | Senile dementia                      | Senile dementia     | +17                                  | 34                | Died, cardiovascular<br>degeneration.                                 |
| 17  | 82            | 53                             | Senile dementia                      | Affective disorder  | +24                                  | 13                | Well orientated, senile<br>weakness.                                  |
| 18  | 78            | 50                             | Secondary dementia                   | Secondary dementia  | +21                                  | 35                | Died, cardiovascular<br>disease.                                      |
| 19  | 72            | 3                              | Melancholia                          | Melancholia         | +14                                  | 18                |                                                                       |
| 20  | 72            | 11                             | Melancholia                          | Melancholia         | +4                                   | 22                | Died, cancer of the<br>prostate.                                      |
| 21  | 66            | 32                             | Delusional, secondary<br>dementia    | Delusional insanity | +39                                  | 18                | Re-graded voluntary,<br>orientation good.                             |
| 22  | 73            | 43                             | Melancholia, secondary<br>dementia   | Secondary dementia  | -1                                   | 40+               |                                                                       |
| 23  | 71            | 26                             | Delusional insanity<br>with dementia | Delusional insanity | +29                                  | 15                | Re-graded voluntary,<br>bright, cheerful and<br>correctly orientated. |

the Mill Hill, was generally lower than potential intellectual capacity, as indicated by the Progressive Matrices performance (Walton and Black, 1958). It was not impossible, therefore, that in the Shapiro and Nelson study the patients were required to learn at a level lower than their intelligence, this producing the misclassifications. A study was then planned in which the subjects were asked to learn the meanings of ten rather than five new words and as such to be learning at a level supposedly more consistent with their intellectual capacity. The results were consistent with the prediction that important differences should be demonstrated between brain-damaged and non-brain-damaged conditions in respect of their speed of learning when level of intelligence was more adequately controlled (Walton and Black, 1957; Walton, 1958).

Although the diagnostic value of the Modified Word Learning Test was unknown at the time of the "Parentrovite" inquiry, its potential value was suggested inasmuch as success on the test appeared superficially to depend on the ability to learn, an ability which appeared to distinguish the functional from the organic patient (Krawiecki, Couper and Walton, 1957). Each of the patients in the "Parentrovite" study was given the Modified Word Learning Test, though the results were not examined in relation to diagnosis until the two-year follow-up study had been completed.

Full details of the method of administration, scoring and normative data of the Modified Word Learning Test are contained in Walton and Black (1957).

RESULTS

Seven of the nine changes in diagnosis in the experimental group were correctly predicted on the basis of the Modified Word Learning Test scores. The optimum cut-off point of 30, established in the earlier inquiry, was used. Using this same cut-off point, the four changes in diagnosis in the control group were correctly predicted. Disregarding the predictive aspects of the study and comparing the final diagnosis (1957) with the M.L.T. completed in 1955, 22 of the 25 people in the experimental group were correctly identified. A cut-off point of 30 was similarly used. Using this same cut-off point all the brain-damaged and non-brain-damaged patients were correctly identified in the control group.

The suggested validity of the scale can be seen by reference to Table III. If the cut-off point is established at 31, than all the non-brain-damaged patients in both the experimental and control group scored less than this. Four of the

TABLE III  
*Distribution of M.L.T. Scores for the Brain-Damaged and Non-Brain-Damaged Subjects in the Experimental and Control Groups*

| M.L.T. Score | Functionals  |         | Organics     |         |
|--------------|--------------|---------|--------------|---------|
|              | Experimental | Control | Experimental | Control |
| 1- 5 .. ..   | 2            |         | 2            |         |
| 6-10 .. ..   | 3            | 3       |              |         |
| 11-15 .. ..  | 1            | 5       |              |         |
| 16-20 .. ..  | 1            | 3       |              |         |
| 21-25 .. ..  | 1            | 1       | 1            |         |
| 26-30 .. ..  | 1            |         | 1            |         |
| 31-35 .. ..  |              |         | 2            | 2       |
| 36-40 .. ..  |              |         | 2            | 1       |
| Over 40 ..   |              |         | 8            | 8       |
| N .. ..      | 9            | 12      | 16           | 11      |

twenty-seven brain-damaged patients were misclassified. Of the total sample of 48 cases, four patients were thus misclassified in terms of the final 1957 diagnosis.

### CONCLUSIONS

The results provide a confirmation of the previously reported work. Important differences were again demonstrated between organic and functional patients in respect of the speed of learning previously unknown verbal material. A high percentage of the organics in the first study were suffering from general cortical damage. In the present enquiry those diagnosed as suffering from senile organic changes presumably were similar in this respect. Both organic groups were the same in showing a great difficulty in learning to the test's required criterion. This difficulty tended not to occur in the functional psychotics of the present enquiry and in the 233 normals and non-brain-damaged psychiatric patients of the first study (Walton and Black, 1957; Walton, 1958).

The testable predictions arising out of the observed correlation between the Memory Scale changes, diagnosis and outcome were therefore confirmed. The Modified Word Learning Test appears of considerable predictive and diagnostic value, particularly with regard to the problem of dementia, when cortical damage is of a general order.

### SUMMARY

The Modified Word Learning Test was administered to 48 senile psychotic patients in 1955, though the results were not examined in relation to diagnosis until a two-year follow-up had been completed.

There was a close correlation between changes in diagnosis and learning test scores. Eleven of the thirteen changes in diagnosis were correctly predicted. Comparing the 1957 diagnosis with learning test scores forty-five of the forty-eight cases were correctly identified when an optimum cut-off point of 30 was used.

The Modified Word Learning Test, based on principles suggested from the vitamin study, appears a valid test of brain-damage at least where the emphasis is on general cortical involvement.

### ACKNOWLEDGMENT

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# EXPERIMENTAL STUDIES OF THE MENTAL SPEED OF SCHIZOPHRENICS

## I. EFFECTS OF A STIMULANT AND A DEPRESSANT DRUG

By

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### INTRODUCTION

It has been clinically observed that psychiatric patients in general (6, 11) and schizophrenic patients in particular (1, 4) show abnormalities of mental speed, being "retarded" or slower than normals on many measures. Confirmatory evidence on this point is to be found but much of the early work on speed of schizophrenic reactivity used measures of speed of motor performance (12, 13) or of reaction time under various conditions (6), ignoring more fundamental slowness of thought processes. The present studies are concentrated on the recent finding that schizophrenics show abnormally slow *mental* speed measured in a problem-solving situation (4, 18, 19). The aim of the investigation was to discover the exact conditions under which this abnormality appears, and, thence, by manipulating the experimental conditions, to be able to bring speed of mental functioning under experimental control. This paper describes the attempt to bring speed under control by means of drugs. A second paper (2) deals with the effect of practice upon mental speed.

Layman (15) conducted an intensive study to measure the changes reported to take place in schizophrenics under the influence of sodium amytal. An improvement in intellectual performance (on the Binet test) was reported. Other workers (17) report an increase in Wechsler Verbal Scale score for schizophrenics with amytal. These, and studies on effects on motor speed, have been repeated elsewhere, but the study of intellectual speed has been largely neglected. One of the few studies in the field is that of Ogilvie (19) who found that amytal improved the speed of problem solving of a group of schizophrenics, while the drug decreased speed of working in a control group of normals.

Osgood (20) suggests that depressant drugs slow down the rate of acquisition of a conditioned response and increase the rate of extinction (10), while the reverse is true of central excitants. Many studies support this suggestion, though only dealing with one type of drug. Thus, Steinberg and Summerfield (27) show that a depressant decreases the rate of acquisition of associations. Despite these suggestive leads from the literature, a survey serves only to indicate the general lack of planning of research on the psychopharmacology of depressant and excitatory drugs. The following experiment was therefore carried out to determine the effects of a central depressant (sodium amytal) and a central stimulant (dexamphetamine sulphate) upon problem-solving speed of schizophrenic subjects.

The literature suggested the following predictions:

1. Central depressants: increase the mental speed of schizophrenics;  
decrease the speed of normal persons;  
do not affect intellectual level of schizophrenics or  
normal persons.
2. Central stimulants: decrease the speed of schizophrenics;  
increase the speed of normal persons.

#### PROCEDURE

The subjects were schizophrenic patients of the Maudsley and Bethlem Royal Hospitals, and students of the Occupational Therapy Departments of the Hospitals. The patients were thus already a select group, not randomly chosen from the general mental hospital population, and the normal subjects were chosen to match them as closely as possible in age and intelligence. The diagnosis of schizophrenia was made by two consultants of the Joint Hospital and no subject was included about whose diagnosis there was any doubt. The patients showed at the time of testing or had shown in the recent past, at least one and more probably two or more of the major symptoms of psychosis found by Lorr, Jenkins and O'Connor (16) in their factorial analysis. Furthermore, the patients were not chronic mental patients, but were early schizophrenics. The period of hospitalization prior to testing varied from a fortnight to 13 months. The average age of the patient group was 25.6 years. Subjects of both sexes were investigated and the sexes were represented equally though there is no evidence that there is a sex difference in speed of mental functioning. The patients were of at least average intelligence as measured by the Nufferno Test of Level of intellectual functioning. They had not received any physical treatment during the six months prior to testing as there is mounting evidence that this has an effect upon speed (9, 14). No patient in the group had undergone psychosurgery, and those who were under a constant regime of drug treatment or sedation were excluded. All patients were rated A or B for co-operation, these being the highest categories on Shakow's (25) criteria.

Subjects were tested individually using the Nufferno Tests of Mental Speed and Level (4, 7, 8). The former gives time scores (mean log. time) and the latter an accuracy score convertible to equivalent I.Q. There are three forms of the Speed Tests—forms AA and AB being parallel simple forms, and form B being more difficult.

#### A. *Effect of Central Depressant—Sodium Amytal*

The performance of twenty-three schizophrenic and seven normal subjects was investigated. The patients were divided into two groups—the drugged (fifteen) and the undrugged (eight). The latter were tested in the same way as the former but were given no drug. Each patient in the drugged group was tested on three consecutive mornings. On the second morning, each took 6 gr. sodium amytal in water. The drug was prescribed by the patient's physician and administered by a nurse of the ward at precisely 10 a.m. (in order to standardize the time interval between ward breakfast and ingestion of the drug).

The experimenter met the patient immediately after 10 a.m. each morning. On the first and third day testing commenced almost immediately. On the second day testing commenced when the patient spontaneously reported feelings

of psychological changes taking place, which occurred after periods ranging from 20 to 45 minutes with an average delay of 31 minutes.

It will be noted that the criterion of drug action is subjective. However, in the absence of such precise measures of sedation threshold as have now been developed (23, 24), it was decided to duplicate the procedure used by Ogilvie (19) who also observed no nystagmus or other physical signs with this dosage and was therefore forced to rely upon the patients' reports. In fact, the dose given was sufficiently large for every patient to report subjective impressions of the drug effect, and rapport was so good that prompt and accurate descriptions of these subjective feelings were forthcoming. Slurring of speech was observed in approximately one-third of the subjects.

Testing consisted of the Nufferno Level Test and Speed tests given on each of the three testing days.

#### B. *Effect of Central Stimulant—Dexamphetamine Sulphate ("Dexedrine")*

Sixteen schizophrenic subjects were chosen in the same way as for the amytal experiment. Results are also available from the group of seven normal subjects previously mentioned. As before, the patients were divided into two groups, drugged and undrugged. The control group was tested as the drugged group but no Dexedrine was given on the second day.

Each patient was tested on three consecutive mornings. At 10 a.m. on the second morning, those in the drugged group took 10 mg. Dexedrine in water. Conditions of administration of the drug and the psychological tests were as for sodium amytal. On the second day testing commenced when the patients spontaneously reported feelings of change, or, failing this, after 45 minutes had elapsed since ingestion of the drug. It was found that many subjects failed to show any effects of the drug and others failed to report subjective feelings attributable to it.

Testing consisted of the Nufferno Level Test given on the first day, and the Nufferno Speed Tests given on each of the three days.

### RESULTS

The results were analysed to determine whether or not there were significant differences in day to day performance as found by Ogilvie (19) and attributed by him to drug effect. Following his analysis, correlated *t*-tests, or *A*-tests (21), were calculated for each of the speed tests. He found significant increases in speed (decrease in mean log. time) at the 0.1 per cent. level (Test AA) and 1 per cent. level (Tests AB and B) from pre-amytal testing to testing under sodium amytal. In the present experiment using sodium amytal the patients were found to improve their scores from Day 1 to Day 2, significantly at the 1 per cent. and 5 per cent. levels for tests AA and AB respectively as shown in Table I.

When comparing results obtained on the second and third days, Ogilvie found decreases in speed. By contrast, the patients in the present experiment showed consistent increases in speed from Day 2 to Day 3, i.e. when sodium amytal was withdrawn. All increases are significant at the 5 per cent. level or beyond. Overall improvement from first to third days was significant for all three speed tests at least at the 1 per cent. level (Table I).

It is apparent, therefore, that Ogilvie's major finding is not confirmed by this study. The improvement in speed scores which he found on testing under



TABLE I  
*Comparison of Scores from Day to Day  
Patients Drugged with Sodium Amytal on Day 2*

| Comparison       | Time in log.-seconds |             | Mean Difference | d.f. | <i>t</i> or <i>A</i> | <i>P</i>                | Significance |
|------------------|----------------------|-------------|-----------------|------|----------------------|-------------------------|--------------|
|                  | First Mean           | Second Mean |                 |      |                      |                         |              |
| Day 1-Day 2:     |                      |             |                 |      |                      |                         |              |
| Speed test AA .. | 1.0692               | 0.9663      | 0.1029          | 7    | 4.5938               | 0.01 > <i>P</i> > 0.001 | 1%           |
| Test AB ..       | 1.1102               | 1.0203      | 0.0899          | 14   | 0.2284*              | 0.05 > <i>P</i> > 0.01  | 5%           |
| Test B ..        | 1.3485               | 1.3336      | 0.0149          | 7    | 0.7450               | <i>P</i> > 0.1          | N.S.         |
| Day 2-Day 3:     |                      |             |                 |      |                      |                         |              |
| Test AA ..       | 0.9663               | 0.8007      | 0.1656          | 7    | 3.7047               | 0.01 > <i>P</i> > 0.001 | 1%           |
| Test AB ..       | 1.0203               | 0.8682      | 0.1521          | 14   | 0.2221*              | 0.05 > <i>P</i> > 0.01  | 5%           |
| Test B ..        | 1.3336               | 1.2502      | 0.0834          | 7    | 4.7931               | 0.01 > <i>P</i> > 0.001 | 1%           |
| Day 1-Day 3:     |                      |             |                 |      |                      |                         |              |
| Test AA ..       | 1.0692               | 0.8007      | 0.2685          | 7    | 6.3300               | <i>P</i> < 0.001        | 0.1%         |
| Test AB ..       | 1.1102               | 0.8682      | 0.2420          | 14   | 0.1050*              | <i>P</i> < 0.001        | 0.1%         |
| Test B ..        | 1.3485               | 1.2502      | 0.0973          | 7    | 3.5071               | 0.01 > <i>P</i> > 0.001 | 1%           |
| Level Test:      | Level Test Score     |             |                 |      |                      |                         |              |
| Day 1-2 ..       | 446.4                | 482         | 35.6            | 14   | 0.2850*              | <i>P</i> > 0.05         | N.S.         |
| Day 2-3 ..       | 482                  | 497         | 14.8            | 14   | 0.8420*              | <i>P</i> > 0.05         | N.S.         |
| Day 1-3 ..       | 446.4                | 497         | 50.6            | 14   | 0.1580*              | 0.01 > <i>P</i> > 0.001 | 1%           |

\* *A*-values (21) which increase in significance as they decrease in size.

sodium amytal is indeed confirmed, but the crucial finding of a return to the original speed on withdrawal of the drug is not repeated here.

Present findings on the Nufferno Level Test are more in line with previous findings. The fifteen drugged patients showed a steady improvement in level from day to day. These improvements are not significant from any one day to the next but overall are significant at the 1 per cent. level (Table I). In a similar calculation Ogilvie found overall improvement in intellectual level of his schizophrenic patients to be significant at the 5 per cent. level.

In view of the discrepant findings—the present results not confirming those of Ogilvie on mental speed—a check was made on the statistical comparability of the groups of patients used in the two researches. The expectation that there were no significant differences between them in age, intellectual level, initial intellectual speed and variances of scores was in fact confirmed. Therefore, with the knowledge that the groups were comparable, further analyses were carried out to investigate the effect of the drug sodium amytal on mental speed of schizophrenics.

Improvement scores, that is, differences in mean log. times from one day to the next day, were calculated for the drugged patients and for the eight schizophrenic control subjects. A comparison of the improvements of these two groups (by uncorrelated *t*-test) showed no significant difference, as shown in Table II. Similarly, when the improvements of the drugged patients are

TABLE II  
*Comparison of Improvement Scores of Patients Drugged with Sodium Amytal, with  
Improvement Scores of Undrugged Patients*

| Comparison    | Time in log.-seconds |           |                 |          |      | Significance |
|---------------|----------------------|-----------|-----------------|----------|------|--------------|
|               | Mean Improvement     |           |                 |          |      |              |
|               | Drugged              | Undrugged | Mean Difference | <i>t</i> |      |              |
| Test AB:      |                      |           |                 |          |      |              |
| Day 1-2 .. .. | 0.0906               | 0.0597    | -0.0309         | 0.3533   | N.S. |              |
| Test AB:      |                      |           |                 |          |      |              |
| Day 2-3 .. .. | 0.0609               | 0.0613    | +0.0004         | 0.0060   | N.S. |              |

compared with those of normals, in six comparisons there is only one significant difference (at the 5 per cent. level). Therefore, from these findings, no significant difference in improvements can be claimed in the day to day speed scores when drugged schizophrenics are compared with undrugged patients or undrugged normal subjects.

Examination of the data from the experiment on Dexedrine yielded similarly negative results. There was a consistent improvement in mean log. times for the drugged group from day to day on all three speed tests, as shown in Table III.

TABLE III

*Comparison of Speed Scores from Day to Day, Patients Drugged with Dexedrine on Day 2*

| Comparison | Time in log.-seconds |             |                 | <i>t</i> or <i>A</i> | <i>P</i>           | Significance |
|------------|----------------------|-------------|-----------------|----------------------|--------------------|--------------|
|            | First Mean           | Second Mean | Mean Difference |                      |                    |              |
| Day 1-2:   |                      |             |                 |                      |                    |              |
| Test AA    | 0.8007               | 0.7171      | 0.0837          | 2.7900               | $0.05 > P > 0.01$  | 5%           |
| AB         | 0.8896               | 0.7636      | 0.1260          | 2.8188               | $0.05 > P > 0.01$  | 5%           |
| B          | 1.2503               | 1.1747      | 0.0756          | 2.2771               | $P > 0.05$         | N.S.         |
| Day 2-3:   |                      |             |                 |                      |                    |              |
| Test AA    | 0.7171               | 0.6748      | 0.0423          | 1.4947               | $P > 0.1$          | N.S.         |
| AB         | 0.7636               | 0.7250      | 0.0386          | 0.8042               | $P > 0.1$          | N.S.         |
| B          | 1.1747               | 1.1096      | 0.0651          | 1.6285               | $P > 0.1$          | N.S.         |
| Day 1-3:   |                      |             |                 |                      |                    |              |
| Test AA    | 0.8007               | 0.6748      | 0.1260          | 0.1822*              | $0.01 > P > 0.001$ | 1%           |
| AB         | 0.8896               | 0.7250      | 0.1646          | 0.2420*              | $0.05 > P > 0.01$  | 5%           |
| B          | 1.2503               | 1.1096      | 0.1584          | 0.2046*              | $0.02 > P > 0.01$  | 2%           |

There are seven degrees of freedom throughout this Table.

\* *A*-values, which are more significant as they decrease in size.

The predicted effect of Dexedrine upon speed of problem solving was not found, and we must conclude that the observed changes in speed scores from day to day are attributable, not to the drug, but to a practice effect.

Comparison of the results from the schizophrenic patients given Dexedrine with those from undrugged patients and normals gave no single significant difference in improvement. Examination of individuals' changes from day to day serve only to show that the effects of the drug Dexedrine on performance in problem-solving speed tests are random, while the overall result of continuous improvement due to practice remains to be investigated (2).

#### DISCUSSION

Dosing schizophrenic subjects, with 6 gr. sodium amytal orally, made no difference to their performance on the Nufferno Speed Tests though an improvement over the whole testing period of three days was observed which could be attributed to practice. Similarly, 10 mg. Dexedrine produced changes in the speed of problem-solving so variable that the only reasonable conclusion is that the effects of the drug are unpredictable. The possibility that the drugs were not in fact acting maximally when testing took place exists, but must be rejected. Testing commenced approximately half an hour after drug ingestion and continued about one and a half hours. The drugs therefore had ample time to become effective.

The further objection may be raised that the experimenter and physician were aware which drug had been given to a patient and when it was given. The study was not planned as a "blind" investigation of the drug effect. In view of the apparent lack of effect of the drugs this factor cannot be held to have influenced the results. Positive findings would have been more suspect and control for this factor would have necessarily followed the first experiments.

It would appear, therefore, unprofitable to continue to investigate drug effects upon intellectual speed. The brain, it seems, is resistant to change in terms of speed of mental functioning in response to both an excitatory and a depressant drug. Resistance to change in conceptual thinking of schizophrenics has also been noted with a mixture of sodium amylal and Dexedrine (22). Other authors agree on the lack of effects of various drugs upon psychological test scores (3, 26), but Franks and Laverty (5) report the opposite in the case of such a simple process as the conditioned eyeblink. Osgood (20) also mentions—with too meagre documentation—that drugs have been found effective in increasing and decreasing the acquisition of conditioned responses, cortical stimulants and depressants being found to have opposite effects.

There is, therefore, great need for further experimentation to show definitely whether or not there is, as suggested by the findings to date, a fundamental difference between simple and complex psychological functioning in changeability under drugs. An experiment comparing the effects of sodium amylal upon problem-solving speed and on conditionability would be of value.

The intrinsic interest, to the clinical psychologist, of the findings of no change in speed measures attributable to the drugs, must not be overlooked. In many situations, examination of a patient is cancelled or delayed, or psychological testing accepted without confidence when it is discovered that the patient is under sedation. The implication of our findings is that sedation is probably irrelevant to cognitive test results. Though there is already some confirmatory evidence on this point, further experiment is needed.

Finally, we may note an important implication of our failure to confirm the preliminary findings of Ogilvie (19) on the effects of sodium amylal on speed of mental functioning in schizophrenics. Isolated experiments with important theoretical and practical implications are too often accepted without question in psychological research. There is much need of repetition and confirmation or refutation of original work. In the present case, it may be pointed out that Ogilvie himself, in a second experiment, could not confirm his earlier results, but he attributed this failure to allowing inadequate time for the drug to take effect (19). In the light of the present findings, the more plausible hypothesis is that the first result was due to an artefact and the second is but further evidence of the real state of affairs.

#### SUMMARY

The effects of a central depressant, sodium amylal, and a central excitant, dexamphetamine sulphate, on speed of mental functioning in schizophrenics, were investigated. Twenty-three schizophrenics and seven normals were given the Nufferno Speed tests on three consecutive days. Fifteen patients were given 6 gr. sodium amylal prior to testing on the second day. Similarly, sixteen schizophrenic patients and seven normals were given the Nufferno Speed tests on three consecutive days. Eight of the patients took 10 mg. dexamphetamine sulphate prior to testing on the second day. Expectations that the depressant drug would increase schizophrenic mental speed and the stimulant decrease speed in these patients, were not confirmed. An improvement in speed scores from day to day was the most consistent finding with both drugs, and is attributable to practice.

The implications of the lack of drug effect are discussed and the need for repetition of experimental work is stressed.



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# EXPERIMENTAL STUDIES OF THE MENTAL SPEED OF SCHIZOPHRENICS

## II. EFFECTS OF PRACTICE\*

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### INTRODUCTION

IN this paper, a further examination is made of the finding that schizophrenics, given a problem-solving task to measure mental speed, showed marked improvements attributable to practice (4).

Preliminary investigation suggested the importance of the effects of both practice and drugs on speed of problem solving. The latter is reported elsewhere (4). There appears in the literature to be agreement that marked improvement is shown by schizophrenic patients after practice, but Huston and Shakow (11, 12) for example, give evidence that this improvement is even more marked for schizophrenics than it is for normals while Hunt and Cofer (9) report the contrary. Huston and Shakow also raise the question of whether or not it is possible, by very extended practice, to bring the performance of schizophrenics to the level of perfection reached by normal subjects after practice. Clarification of these points is necessary.

Examination of the literature in combination with the preliminary investigations led to the following predictions:

- i. That improvements in speed scores attributable to daily practice would be greater among schizophrenics than among normal subjects.
- ii. That, after practice, schizophrenic problem-solving speed would not be significantly slower than that of normal subjects without practice.

### PROCEDURE

As in the previous study (4) the subjects were patients and staff of the Maudsley and Bethlem Royal Hospitals. The patients were young early schizophrenics of at least average intelligence and the normal subjects were chosen to match them in age and intelligence. Patients had not recently had physical treatment or sedation, and co-operation was good being rated A or B on Shakow's (18) criteria.

All subjects were tested individually using the Nuffern Tests of Mental Speed and Level (5, 6, 7). The former gives time scores (mean log. time) and the latter an accuracy score convertible to equivalent I.Q. There are three forms of the Speed Tests, forms AA and AB being parallel simple forms, and form B being more difficult.

Eight schizophrenics and seven normals were tested each on five consecutive days. Testing commenced at the same time of day on each occasion

\* A preliminary report (3) of this work was read at the 1957 Annual Conference of the British Psychological Society at St. Andrews.

but the time required for testing varied greatly with the individuals. Testing therefore lasted between one hour and three hours per day among the patients and between three-quarters of an hour and an hour and a quarter per day for the normals.

### RESULTS

Examination of the results showed primarily a steady improvement in speed from day to day. After five days' practice both groups showed an improvement in speed scores which was significant at the 1 per cent. level or beyond (by one-tail *t*-test), and this improvement was consistent for all three speed tests. Since the subjects were given no encouragement to further spurts of speed, no rewards, or drug stimulants, the improvement found in speed scores of normals and schizophrenics alike can safely be attributed to practice. In general, a steady improvement in speed occurred throughout the series of five consecutive practice days, but the extent of improvement from day to day was rather variable. However, the establishment of the fact of speed improvement permits a comparison of the two groups (normal and schizophrenic) with respect to the amount of improvement.

Firstly, the difference between the patients and normals was compared at the beginning and at the end of the practice period. Table I shows that at the start of the practice period, the groups differed significantly in all speed scores,

TABLE I

*Comparison of Schizophrenics and Normals with Respect to Initial Speed Scores on the Three Nufferno Speed Tests. Time in log.-seconds*

| Test           | Schizophrenics |  | Normals |  | Mean Difference | 2-tail <i>t</i> | Significance |
|----------------|----------------|--|---------|--|-----------------|-----------------|--------------|
|                | Mean           |  | Mean    |  |                 |                 |              |
| AA .. ..       | 1.0692         |  | 0.7428  |  | 0.3264          | 4.8026          | 0.1%         |
| AB .. ..       | 1.0411         |  | 0.8622  |  | 0.1789          | 2.4176          | 5%           |
| Difficult B .. | 1.3485         |  | 1.0988  |  | 0.2497          | 4.4148          | 0.1%         |

There are 13 degrees of freedom in each case.

the normal subjects being faster in every case. This is consistent with previous work (e.g. 1, 2, 5, 8, 11, 14, 17). On the other hand, comparison of the speeds of the two groups after five days' practice, to be found in Table II, shows that,

TABLE II

*Comparison of Schizophrenics and Normals with Respect to Speed Scores after Five Days' Practice. Time in log.-seconds*

| Test     | Schizophrenics |  | Normals |  | Mean Difference | 2-tail <i>t</i> | Significance |
|----------|----------------|--|---------|--|-----------------|-----------------|--------------|
|          | Mean           |  | Mean    |  |                 |                 |              |
| AA .. .. | 0.6748         |  | 0.4298  |  | 0.2450          | 3.3273          | 1%           |
| AB .. .. | 0.7250         |  | 0.5298  |  | 0.1952          | 4.2759          | 0.1%         |
| B .. ..  | 1.1096         |  | 0.8902  |  | 0.2194          | 3.0540          | 5%           |

There are 13 degrees of freedom in each case.

though on the whole the normals maintained a significant superiority over the schizophrenics, the differences between the two groups had decreased. Thus, the comparison of the groups at the beginning and at the end of the practice indicates that their rate of improvement with practice is not equal, but fails to confirm the expectation that after practice there would be no significant difference between the two groups in speed.



The speed of the patients on the fifth day was also compared with the speed of the normal subjects on the first day as shown in Table III. The

TABLE III

*Comparison of Speed Scores of Schizophrenics after Five Days' Practice with Speed Scores of Normals on First Testing. Time in log.-seconds*

| Test |       | Schizophrenics<br>Mean | Normals<br>Mean | Mean<br>Difference | 2-tail <i>t</i> | Significance |
|------|-------|------------------------|-----------------|--------------------|-----------------|--------------|
| AA   | .. .. | 0.6748                 | 0.7428          | 0.0680             | 0.8776          | N.S.         |
| AB   | .. .. | 0.7250                 | 0.8622          | 0.1372             | 2.5422          | 5%           |
| B    | .. .. | 1.1096                 | 1.0988          | 0.0108             | 0.1536          | N.S.         |

There are 13 degrees of freedom in each case.

differences were not significant, except that the schizophrenics after five days' practice actually exceeded the normal starting score on form AB of the Nufferno Speed Tests and this difference is significant at the 5 per cent. level. These results confirm the prediction that, by relatively limited practice, a schizophrenic group can eliminate the speed discrepancy existing between themselves and normals of comparable age and intellectual level.

Secondly, a comparison of the improvements made by the two groups was carried out, using difference scores (e.g. Day 1 score minus Day 5 score) as measures of improvement.

In fact the mean improvements of schizophrenics, as shown in Table IV,

TABLE IV

*Comparison of Improvement Scores of Schizophrenics and Normals after Three and Five Days' Speed Practice. Time in log.-seconds*

| Test     |    | Schizophrenics<br>Mean<br>Improve-<br>ment | Normals<br>Mean<br>Improve-<br>ment | Mean<br>Difference | 2-tail <i>t</i> | Significance |
|----------|----|--------------------------------------------|-------------------------------------|--------------------|-----------------|--------------|
| Day 1-3: |    |                                            |                                     |                    |                 |              |
| AA       | .. | 0.2685                                     | 0.0897                              | 0.1788             | 3.506           | 1%           |
| AB       | .. | 0.1515                                     | 0.1387                              | 0.0128             |                 | N.S.         |
| B        | .. | 0.0982                                     | 0.0768                              | 0.0214             |                 | N.S.         |
| Day 1-5: |    |                                            |                                     |                    |                 |              |
| AA       | .. | 0.3944                                     | 0.3129                              | 0.0815             | 1.032           | 1%           |
| AB       | .. | 0.3161                                     | 0.3324                              | 0.0163             |                 | N.S.         |
| B        | .. | 0.2390                                     | 0.2086                              | 0.0304             |                 | N.S.         |

are in every case greater than the mean improvements of the normals and two of these comparisons (on the simple form AA) reach the 1 per cent. level of significance.

The results on the Nufferno Level Test contrast with this finding. Both groups show marked improvement in level after practice but when improvements are compared it is found that the normals' improvement is greater than that of schizophrenics. No significant difference in the magnitude of level improvement is found between the two groups.

A second experiment was carried out to discover whether or not these findings could be generalized beyond the test used. Eight further schizophrenic subjects were tested on three consecutive days in the manner described above. Testing was, however, limited to form AA of the Speed tests until the third day when form AB (the equivalent form) was also given. Thus we have results for

schizophrenics on a simple speed test after three days' practice on the equivalent form. Comparison of the scores on form AA on the first day with scores on form AB on the third day shows the difference to be significant at the 5 per cent. level, suggesting that practice on one speed test will improve scores on another similar but unfamiliar test.

#### DISCUSSION

The reader who has difficulty in relating log. seconds to actual time taken may be reassured that the results were also evaluated using time in seconds as the basis for calculation. The superior improvement of the schizophrenics was even more marked under these conditions. However, the log. second score is to be preferred as it is at once a normalizing procedure and the score which lends itself most readily to theorizing in the area of the nature of the speed, level and continuance components of intelligence (6).

The present findings, that schizophrenics improve more with practice than do normals, is a corroboration of and extension of the findings of Huston and Shakow (11, 12) who, however, failed to comment on this aspect of their results. They showed that when schizophrenic and normal subjects are allowed to practise a motor task, both groups improve in speed and ability, and that schizophrenics—who originally obtain poorer scores—rapidly improve to the starting level of normal subjects. It is now shown that strikingly similar results can be obtained when normal and schizophrenic subjects are compared on *speed* scores, using a problem-solving task to measure speed of mental functioning. Retardation or slowing of the thought processes has been noted as a symptom in schizophrenia (e.g. 1). It is therefore of some importance to measure this aspect of psychological functioning directly and improvements in it are noteworthy.

Contrary results on the ability of schizophrenics to improve have been reported (9), but the diversity of findings can be attributed in part to the recording of improvements in terms other than speed, i.e. in scores based on accuracy or number of errors. Contrary results may also be due to differences in the relative massing or spacing of the practice in question. Examining eight studies on improvement of schizophrenics with practice (noted below) it is found that when they are divided into experiments with massed practice and spaced practice the discrepant results are to some extent explained. By "massed practice" practice within a period of a day or less is understood, for the present purpose, while "spaced practice" includes those experiments spread over two or more days. Of seven experiments reported using spaced practice (as defined above), two show great improvements among schizophrenics but make no comparison with normals (2, 13), four show greater improvement in schizophrenics than in normals (11, 12, 14) and one is equivocal (15). On the other hand, of five experiments on massed practice, two show schizophrenics' improvement to be less than normals' (11, 19), two are equivocal (12) and one reports equal improvement for schizophrenics and normals (15). The present results, on daily practice ("spaced practice" on the above definition), are in line with the general trend of results from similarly spaced practices, i.e. show greater improvement among schizophrenics than normals.

It is of interest that schizophrenic subjects appear to improve more with practice than normals do, when the practice is spaced, but not when it is massed. Normal subjects are known to perform (learn and remember) better under conditions of spaced practice and this has been attributed to the dis-

sipation during rest of reactive inhibition ( $I_R$ ) accumulated during the working period. That there is a greater than normal difference in learning under the two conditions shown by schizophrenics suggests that schizophrenic subjects are more susceptible to reactive inhibition than are normals. There is already some evidence to support this hypothesis (19) and further work is in progress to clarify the point. Increased susceptibility to reactive inhibition might be postulated as a contributory cause of schizophrenic slowness, but, lacking further confirmation it is at present put forward tentatively as an hypothesis for testing.

We may therefore conclude that:

1. Where measures of psychological speed are taken, schizophrenic subjects respond to daily practice with greater improvement than normal.
2. After relatively little practice, schizophrenic subjects can improve their scores on speed of mental functioning to the level attained by normal subjects without practice.
3. Improvement in speed scores is not altogether specific to the test given, and shows a transfer effect to a similar but unfamiliar test.

These conclusions may have therapeutic relevance for some hospitalized schizophrenics. It can be hypothesized that intellectual slowness is a contributory cause of the confused states characteristic of psychosis, and that training can improve this aspect of psychological functioning. While no claim is made that improvement in speed of mental functioning can be a cure for schizophrenia, the possibility exists that on this basis a programme of treatment may be worked out leading to the rehabilitation of some of these patients.

#### SUMMARY

In an attempt to improve the speed of mental functioning of schizophrenics, a group of eight patients was given practice in tests of intellectual speed and level for five consecutive days. Significant improvements attributable to practice were noted, particularly in the speed tests. A similarly marked improvement in mental speed scores was observed in a comparable group of seven normal subjects also tested on five consecutive days. A comparison of the two groups showed that the improvement in mental speed of the schizophrenics was superior to that of the normals, but this was not true in the level test. An experiment on the "transfer" of the found improbability of the schizophrenic subjects indicated that the improvement can be generalized, at least to similar tests of mental speed.

The results are examined in terms of the concept of reactive inhibition, and the implications of the findings for the treatment of schizophrenics briefly noted.

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# MEASUREMENTS OF EFFECTS OF HYALURONIDASE IN INSULIN COMA TREATMENT

By

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## INTRODUCTION

HYALURONIDASE, the "spreading factor" is widely used today to aid the distribution and absorption of fluids injected at various sites into body tissues. It is derived from the head of the male sperm cell which by its action dissolves hyaluronic acid in the "shell" surrounding the female egg cell and thereby allows spermal penetration and conception; generally speaking it dissolves the ground substance between cells. The most remarkable usage is in paediatrics where it allows for quick replacement of lost fluid and salt in gastro-enteritis, obviating the need to find veins, and thereby saving practically all cases from death by dehydration. There are many other uses.

Hyaluronidase once injected into body tissue is quickly absorbed into the blood-stream and inactivated by anti-hyaluronidase. These effects have been summarized by Wyburn and Bacsich (1950).

It was hoped that this substance might help to make the deep insulin coma treatment of schizophrenia more predictable and less hazardous, and also that it would assure the complete absorption of the injected insulin at whatever tissue plane, thereby abolishing or markedly reducing the after-shocks numerically.

## REVIEW OF LITERATURE

Demay *et al.* (1953) examined the effect of hyaluronidase on 6 patients—reduction of dosage, quicker and deeper coma, more rapid waking and absence of after-shock are claimed. Unfortunately no statistical data are given, no control cases are employed and no measurements *re* waking-up times are quoted.

Blandin *et al.* (1955) in a series of 25 cases make similar claims. If one takes the averages of the first and last coma-doses, the hyaluronidase cases appear to require less insulin. (In general the dosages of insulin administered by these authors are remarkably low.) No criteria are given as to which features determine the onset of coma.

Gysin and Wilson (1954) added hyaluronidase to insulin after approximately 10 comas and then reduced the insulin dosage. There is no indication in their report that the insulin dose had already been reduced to a lower level as is usually possible at this stage of the course. The number of i.v.-glucose

interruptions necessary in their unit appear rather high. No figures are given for the claim of a shortened sopor but clinical impressions are included.

Holden and McGuinness (1957) use each patient as his own control in a similar way to Gysin and Wilson. Their numerical data suggest that nothing much was gained by the addition of hyaluronidase but the "clinical impressions" are favourably inclined.

Tyndel (1956) claims reduction of pre-coma time by one-third (presumably this means the time between injection and coma), although some of the other statements are difficult to follow, e.g. "the average duration of therapy was reduced from 61 to 55½ days". Almost all authors claim a reduction in "restlessness" during treatment.

#### TECHNICAL PROBLEMS

It is quite obvious that it is very difficult to measure and compare all the factors mentioned in these reports, especially "restlessness". From our observations three different types of "restlessness" may occur either in the soporphase or during the waking-up period: (a) twitching of the limbs similar to the clonic stage of an epileptic fit but without proper rhythm—i.e. jactitations, (b) what may be described as large-scale writhings and contortions of the whole body, and (c) hyper-extension rigidity.

We would suggest that (a) is due to cortical/subcortical activity, (b) is due to mid-brain activity (righting reflex type of movement) and (c) due to medullary and spinal activity (stretch reflex type). Unless one goes very much into details and measures amplitudes of movement or durations of the various types of motor activity it is probably wise to abstain from categorical statements about the hyaluronidase effects on these. From the data given it appears that this has not been done by the various authors. For reference as to criteria see the excellent and detailed study by Frostig (1940) and also by Kueppers (1937). Our staffing facilities did not permit such measurements in all cases. In the current study impressions are given below (see under Restlessness).

#### TECHNIQUE

The insulin injection was given at 7.30 a.m. with the object of inducing a coma at 10 a.m., i.e. after 150 minutes. (This may explain to some degree our relatively high doses, since Frostig and others aim for the coma to appear approximately 270 minutes after the insulin injection "in the 2nd half of the 5th hour".)

Again differing from Frostig, our patients remained in the state of "complete" coma for 30 minutes before being interrupted in the usual way by tube-feeding, instead of being fed at the onset of this stage.

To assess some of the effects of hyaluronidase we measured its influence on:

- (a) Length of sopor.
- (b) Time of onset of coma.
- (c) Stability of onset, i.e. the measurement of the intervals of onset of coma from day to day.
- (d) Waking duration, i.e. time between tube-feeding and the patient being fully awake (even if still slightly disorientated).
- (e) Number of intravenous interruptions of coma necessary.
- (f) Number of epileptiform fits.



- (g) Number of after-shocks—here are included not only intravenous glucose medications which become necessary, but slight reactions such as sweating, excessive hunger and light headedness have been counted.
- (h) As the aim in the unit was to induce the onset of coma at 10 a.m. dosage was altered mainly according to this requirement. We have therefore also compared the average insulin dosages of those days when hyaluronidase was administered (H days) with those days when hyaluronidase was not used (non-H days), for each patient and constructed average insulin dosage curves for the H days and non-H days. These two curves are opposed to the average dosage curve of 30 control cases, matched approximately as to sex, age, body build, previous personality and body weight, mode of onset, duration and type of psychosis.

Thirty-two schizophrenic patients received hyaluronidase 500 I.U. together with insulin in one injection (deep intra-muscularly, changing the site daily). The patients were classified as follows:

1. *Pilot Group*. Eight patients served as a pilot group and received the additional drug at various stages during the course, for a few days only, varying from 4–19 days at the most.

2. *Alternate Days Group*. Eight patients received hyaluronidase from the first injection onwards every second day. (Since it is known that the action of hyaluronidase is utilized at the site of the injection, there is no overlap from one day to the other. Our observations tend to confirm this.)

3. *Alternate Weeks Group*. Eight patients received the additional drug from Monday to Saturday of one week (Sunday being a rest day) followed by a week with insulin alone, and so on alternately.

4. *Sixteenth to Thirtieth Coma Group*. Eight patients received the hyaluronidase from their 16th to their 30th coma only; on both parts of the course before and after these 15 days insulin alone was given.

For each of the 32 patients the following curves were constructed:

- (a) Dosage curve.
- (b) Onset of twitching.
- (c) Onset of sopor.
- (d) Onset of coma.
- (e) Feeding.
- (f) Waking up.

Entries in the daily sheet, from which the curves were constructed, were made to the nearest 5 minutes. The curves therefore also express 5-minute intervals. One would expect that, if the claims for hyaluronidase were valid, there would be definite breaks in these curves, depending on the administration or discontinuation of the drug.

Altogether 630 injections of hyaluronidase were given. The above 8 measurements were compared for the total, and also for each group separately. The groups were well matched as to the criteria quoted for the 30 control cases.

## HYPOTHESES AND DATA

### HYPOTHESIS I

#### *Duration of Sopor*

The duration of sopor, i.e. the interval between the onset of sopor and coma, is not significantly influenced by the addition of 500 U. of hyaluronidase to the daily intramuscular injection of the coma-producing dose of insulin.

Definition of Onset of Sopor

- (a) Patient is unconscious but at such a shallow level that he still responds to certain tactile stimuli, but not to auditory stimuli and cannot be properly roused.
- (b) He is usually sweating, restless and twitching. His muscles are hypertonic.
- (c) He is amnesic.

Criteria for Onset of Coma

- (a) Patient is unconscious.
- (b) He does not react to stimuli; (glabellar, tapping, visual, tactile, etc.).
- (c) Muscles are mainly flaccid.
- (d) Tendon reflexes weak or absent.
- (e) Plantar reflexes absent or extensor.

For each of the 32 patients the length of sopor during the "H days" was compared with that for the "non-H days" and analysed for statistical significance with the usual formula.

From Table I it can be seen that the length of sopor was shortened (calculating averages for each case and comparing an equal number of H days with non-H days) in 17 out of 32 cases, lengthened in 13 and no difference in 2. Even if there is a preponderance of the shortened cases and even if this were statistically significant it would obviously be of only limited clinical importance.

For three individual patients the mean duration of sopor was ten minutes shorter under hyaluronidase than when the same patients were not under the additional drug. This difference was significant at the  $P=0.05$  level. However, for two other patients (II/5, III/8) the effect of hyaluronidase was to significantly increase the mean duration of sopor by 11 and 10 minutes, respectively. In no other case was the mean sopor duration significantly changed by the additional drug.

Taken as a whole the mean sopor duration times under hyaluronidase did not differ significantly from the sopor duration times of non-hyaluronidase days. This appears from the following table, for which  $\chi^2$  is obviously not significant:

|            | <40   |    |    | > 39  |    |    |
|------------|-------|----|----|-------|----|----|
| H. Group   | ..    | .. | .. | 15    | 17 | 32 |
| N.H. Group | ..    | .. | .. | 15    | 17 | 32 |
|            | <hr/> |    |    | <hr/> |    |    |
|            | 30    |    |    | 34    |    |    |
|            | <hr/> |    |    | <hr/> |    |    |
|            |       |    |    | 64    |    |    |

HYPOTHESIS II

Time of Onset of Coma

The time of onset of the insulin coma is not significantly expedited by the addition of hyaluronidase (the injections were given at 7.30 a.m.).

Method

Averages of onset were arrived at comparing equal numbers of H and non-H days.

TABLE I  
Average Measurements on 32 Patients Undergoing Insulin Coma Treatment

| Patient No.                 | 1  | 2  | 3     |     | 4             |         | 5                  |       | 6               |     | 7                   |      | 8                 |       | 9  |     |       |
|-----------------------------|----|----|-------|-----|---------------|---------|--------------------|-------|-----------------|-----|---------------------|------|-------------------|-------|----|-----|-------|
|                             |    |    | Sopor |     | Onset of Coma |         | Stability of Onset |       | Waking Duration |     | Intravenous Glucose |      | Epileptiform Fits |       |    |     |       |
|                             |    | N  | H.    | NH. | Diff.         | H.      | NH.                | Diff. | H.              | NH. | Diff.               | H.   | NH.               | Diff. | H. | NH. | Diff. |
| I. Pilot Group:             |    |    |       |     |               |         |                    |       |                 |     |                     |      |                   |       |    |     |       |
| 1                           | .. | 6  | *-33  | 23  | -10           | 10-37   | 10-37              | 0     | *+21            | 43  | +22                 | 10   | 9                 | -1    | 0  | 0   | 0     |
| 2                           | .. | 7  | 38    | 38  | 0             | 9-33    | 9-43               | +10   | 10              | 18  | +8                  | 7    | 11                | +4    | 0  | 0   | 0     |
| 3                           | .. | 11 | 38    | 33  | -5            | *+9-79  | 10-04              | +15   | 7               | 7   | 0                   | 13   | 11                | -2    | 0  | 0   | 0     |
| 4                           | .. | 9  | 40    | 37  | -3            | 10-04   | 10-11              | +7    | 23              | 23  | 0                   | 17   | 19                | +2    | 0  | 0   | 0     |
| 5                           | .. | 9  | 31    | 36  | +5            | *+9-58  | 10-28              | +30   | 33              | 35  | +2                  | 28   | 22                | -6    | 5  | 0   | 0     |
| 6                           | .. | 17 | 37    | 30  | -7            | *-10-42 | 10-23              | -19   | 17              | 12  | -5                  | 6    | 6                 | 0     | 0  | 0   | 0     |
| 7                           | .. | 19 | 47    | 42  | +5            | 9-47    | 9-54               | +7    | 16              | 13  | -3                  | 7    | 7                 | 0     | 0  | 1   | 1     |
| 8                           | .. | 17 | 50    | 41  | -9            | 10-06   | 10-05              | -1    | 16              | 15  | -1                  | 18   | 17                | -1    | 6  | 7   | 1     |
| II. Alternate Days Group:   |    |    |       |     |               |         |                    |       |                 |     |                     |      |                   |       |    |     |       |
| 1                           | .. | 25 | 40    | 47  | +7            | *+9-57  | 10-12              | +16   | *+14            | 32  | +18                 | 10   | 11                | +1    | 2  | 1   | 1     |
| 2                           | .. | 24 | 50    | 52  | +2            | 10-24   | 10-30              | +6    | 20              | 15  | -5                  | 13   | 14                | +1    | 0  | 0   | 0     |
| 3                           | .. | 23 | 32    | 28  | -4            | 9-53    | 10-06              | +13   | *+18            | 34  | +16                 | 3    | 2                 | -1    | 0  | 0   | 0     |
| 4                           | .. | 24 | 34    | 37  | +3            | 9-45    | 9-51               | +6    | 17              | 19  | +2                  | 11   | 11                | 0     | 0  | 0   | 0     |
| 5                           | .. | 24 | *+31  | 42  | +11           | 10-47   | 10-55              | +8    | 14              | 16  | +2                  | 11   | 11                | 0     | 0  | 0   | 0     |
| 6                           | .. | 23 | 35    | 36  | +1            | 10-20   | 10-25              | +5    | 23              | 35  | +12                 | 23   | 25                | +2    | 4  | 3   | 1     |
| 7                           | .. | 22 | *-57  | 47  | -10           | 9-33    | 9-36               | +3    | 21              | 24  | +3                  | *+13 | 20                | +7    | 0  | 0   | 0     |
| 8                           | .. | 25 | 55    | 63  | +8            | 10-40   | 10-50              | +10   | 20              | 19  | -1                  | 21   | 21                | 0     | 1  | 0   | 0     |
| III. Alternate Weeks Group: |    |    |       |     |               |         |                    |       |                 |     |                     |      |                   |       |    |     |       |
| 1                           | .. | 24 | 45    | 45  | 0             | 9-53    | 10-06              | +13   | 12              | 19  | +7                  | 21   | 20                | -1    | 0  | 0   | 0     |
| 2                           | .. | 24 | 36    | 40  | +4            | 10-12   | 10-18              | +6    | 14              | 15  | +1                  | 19   | 18                | -1    | 0  | 0   | 0     |
| 3                           | .. | 23 | 45    | 46  | +1            | 9-31    | 9-40               | +9    | 11              | 11  | 0                   | 20   | 21                | +1    | 0  | 1   | 0     |
| 4                           | .. | 21 | 40    | 46  | +6            | 10-16   | 10-29              | +13   | 16              | 20  | +4                  | 13   | 16                | +3    | 2  | 0   | -2    |
| 5                           | .. | 24 | 48    | 55  | +7            | 10-06   | 10-05              | -1    | 17              | 10  | -7                  | 15   | 13                | -2    | 1  | 0   | 0     |
| 6                           | .. | 27 | 31    | 37  | +6            | 9-50    | 9-43               | -7    | 16              | 13  | -3                  | 19   | 20                | +1    | 0  | 0   | 0     |
| 7                           | .. | 21 | 37    | 32  | -5            | 9-55    | 10-05              | +10   | 12              | 16  | +4                  | 20   | 17                | -3    | 2  | 3   | 0     |
| 8                           | .. | 24 | *+41  | 51  | +10           | 9-33    | 9-40               | +7    | 7               | 10  | +3                  | 17   | 14                | -3    | 1  | 2   | 1     |
| IV. 16th-30th Coma Group:   |    |    |       |     |               |         |                    |       |                 |     |                     |      |                   |       |    |     |       |
| 1                           | .. | 15 | 54    | 50  | -4            | 9-59    | 9-49               | -10   | 22              | 19  | -3                  | 7    | 8                 | +1    | 0  | 0   | 0     |
| 2                           | .. | 15 | 48    | 50  | +2            | 10-27   | 10-25              | -2    | *+19            | 23  | +14                 | 10   | 21                | +1    | 0  | 0   | 0     |
| 3                           | .. | 15 | 33    | 26  | -7            | 9-54    | 10-04              | +10   | 24              | 31  | +7                  | 14   | 18                | +4    | 0  | 0   | 0     |
| 4                           | .. | 15 | *-49  | 39  | -10           | 10-21   | 10-25              | +4    | *-18            | 7   | -11                 | 13   | 14                | +1    | 5  | 11  | -4    |
| 5                           | .. | 15 | 61    | 63  | +2            | 9-58    | 10-05              | +7    | 21              | 26  | +5                  | 12   | 16                | +4    | 0  | 0   | 0     |
| 6                           | .. | 15 | 38    | 31  | -7            | 10-13   | 10-19              | +6    | 10              | 12  | +2                  | 18   | 22                | +4    | 0  | 0   | 0     |
| 7                           | .. | 15 | 54    | 61  | +7            | 10-10   | 10-17              | +7    | 17              | 25  | +8                  | 20   | 19                | -1    | 0  | 0   | 0     |
| 8                           | .. | 15 | 66    | 63  | -3            | 9-57    | 10-04              | +7    | 27              | 23  | -4                  | 23   | 25                | +2    | 4  | 8   | +4    |

## REMARKS

Column 1 contains the four groups of 8 patients each, the name given to each group indicating in which manner the patients received the hyaluronidase in addition to the insulin. 2, "N" gives the actual number of "hyaluronidase days" for each patient, and also the number of non-hyaluronidase days with which they have been compared. 3, "Sopor" is taken from the beginning of sopor to the onset of coma (both as defined in the article). The figures mean minutes and are averages. 4, "Onset" means time of onset of coma, again in averages. 5, "Stability" means the average for each patient of the difference from H. day to H. day (and non-H. day to non-H. day respectively), i.e. a measure of the predictability of the time of onset. (Theoretically one would expect these figures in minutes to be smaller on the H. days, which in fact they are.) 6, "Waking Duration" means the averages in minutes from time of nasal feed to rational waking state, for each patient. 7, "Intravenous Glucose" i.e. those days on which i.v. glucose was needed to either aid waking (usually given if patient is not awake 20 minutes after nasal interruption of coma) or to terminate distress. 8, "Fits" means epileptiform fits occurring during the days under consideration. 9, "After shocks" relates to the minor symptoms of hypoglycaemia which occurred in the days on. Again equal numbers of "H" and "non-H" days have been compared for each patient. "H" and "NH" in columns 3-9 indicate the averages for the days of comparison, i.e. total divided by N on each side (in group IV [16th-30th coma] the 7 comata before coma 16 plus the 8 comata after coma 30 have been compared with the "Hyalase"—comata 16-30, i.e. the same number—15).



*Result*

From the table it can be seen that in 25 out of the 32 cases such a precipitation of onset in fact took place, in 6 cases a postponement and in one there was no change. If one takes the average of the averages—a questionable method—one would arrive at a mean precipitation of coma for each of the 630 H days by 6 minutes. Whilst there is undoubtedly a change produced by the hyaluronidase in the desired direction it is not of great clinical importance.

For two individual patients the mean time of onset of coma under hyaluronidase was significantly less than the mean time of onset for the same patients when not under the additional drug (Cases I/3 and II/1, Table I). In one other case (I/5) the mean reduction is sufficiently marked to approach statistical significance and in one case (I/6) the effect of the drug is markedly to increase the time of onset to a degree that also approaches significance.

Statistical tests applied to individual scores of the remaining 28 patients failed to indicate any individually significant change. We have noted that the injection was given at 7.30 a.m. on each occasion with the object of inducing a coma at about 10 a.m. If the average coma time for the H days and the N.H. days are considered then the mean Coma Time for the H. group occurs before 10 a.m. more frequently than is the case for the N.H. groups ( $\chi^2=5.32$ , significant at  $P=0.05$  level). The actual table is as follows:

|            |    |    |    | <i>Mean Coma Time</i> |               |          |
|------------|----|----|----|-----------------------|---------------|----------|
|            |    |    |    | Before 10 a.m.        | After 10 a.m. |          |
| H. Group   | .. | .. | .. | 17                    | 15            | 32       |
| N.H. Group | .. | .. | .. | 8                     | 24            | 32       |
|            |    |    |    | <hr/> 25              | <hr/> 39      | <hr/> 64 |

## HYPOTHESIS III

*Stability of Onset of Coma*

The addition of hyaluronidase has no stabilizing effect on the onset of coma, i.e. if hyaluronidase has a positive effect then the coma would occur more frequently at about the same time than when hyaluronidase is not given, diminishing the amplitude between the times of onset and therefore aiding predictability.

Averages were calculated for the differences in minutes of the onset on the H days and compared with the average differences between an equal number of non-H days. It was found that in 19 patients a diminution of the amplitude occurred, in 3 it was unchanged and in 10 it was increased. It appears that hyaluronidase has a favourable effect, even if it might not be of great clinical significance. The calculated value of  $\chi^2$  for these data does not reach statistical significance although the trend is apparent.

For four individual patients the mean rating of stability of onset was significantly increased by the addition of hyaluronidase (Cases I/1, II/1, II/3 and IV/2). In one other case (IV/4) however, the effect of hyaluronidase was to reduce significantly the mean rating of onset of stability. Statistical tests applied to the remaining 27 patients failed to indicate any individually significant change.

## HYPOTHESIS IV

*Waking Time*

The time taken between nasal interruption of the coma and awakening of the patient is not significantly shortened.

Again averages of waking time were calculated in minutes and it was found that these were shorter in 17 cases, unchanged in 5 cases and lengthened in 10 cases (see column 6 of Table I).

For two individual patients only (Cases II/7 and IV/5) the addition of hyaluronidase to the injection reduced the average waking duration by 7 minutes—a difference that is significant at the 0.05 level of P.

### *Miscellaneous Points*

From the table it will be seen that the necessity for intravenous interruption of coma did not arise in 12 cases, either when hyaluronidase was administered or when not. In the remaining 20 cases, the necessity arose more frequently with hyaluronidase in 11 cases, was diminished in 7 cases and equal in 2 cases. During the 630 H days a total of 45 i.v. glucose interruptions were necessary as opposed to only 38 during the same number of non-H days. In this respect in our trial, hyaluronidase appears slightly disadvantageous. A statistical analysis is obviously unwarranted.

As regards epileptiform fits it will be seen from Table I that in the 32 cases, during the days under consideration fits occurred in 19 of the patients. In 11 cases there were fewer fits on H days, in 1 case there was no difference and in 7 cases there occurred more fits on H days. Altogether 114 fits occurred during the time under consideration for the 32 patients.

This situation appears slightly in favour of hyaluronidase addition to the insulin dose, although the distribution is obviously insignificant.

After-shocks were very rarely seen throughout. In view of the very high incidence reported from other units we may be allowed to attribute this favourable picture of our unit to the excellent nursing care. During 1,260 coma days ( $630 \times 2$ ) altogether 15 after-shocks occurred, 10 during H days and 5 during N.H. days. In view of the small overall incidence no comment is justified.

One patient from group IV (who had hyaluronidase added from the 16th to the 30th coma) had to be re-admitted in another psychotic phase (patient IV/4). This time she had hyaluronidase from the first to the last day of the course. Her average dose was 296 units (264 units), the average duration of sopor 45 minutes (44 minutes), average time of onset 10.29 a.m. (10.27 a.m.), stability of onset (as defined above) 12 minutes (13 minutes) waking duration 19 minutes (13 minutes); she had 11 epileptic fits (6) and once needed intravenous glucose interruption of the coma (zero). The figures in brackets are the figures relating to the first course. It is only fair to say, however, that she was the one patient who had already reacted unfavourably to hyaluronidase during the previous course (see Table I, patient IV/4).

We are unable, with our criteria for the reduction of the dose of insulin during the course of treatment (that is with an aim to achieve the onset of coma at 10 a.m.), to support the claims of other authors in this respect. Had we chosen different criteria the picture *might* have been different also, but in view of the lack of information and detailed measurements provided in other accounts, we are unable to comment on this discrepancy. The three curves in Figure 1 show that there was no difference between the H days and N.H. days or the control group as regards dosage. Minor reductions might have been possible. We would like to add that the "average coma dose" has been arrived at by adding all the insulin doses given during the whole of the course, that is including the introductory stepping up of the dosage until coma was reached, and this figure has then been divided by 50. This in part explains the relatively high figures.

# AVERAGES OF INSULIN DOSAGE

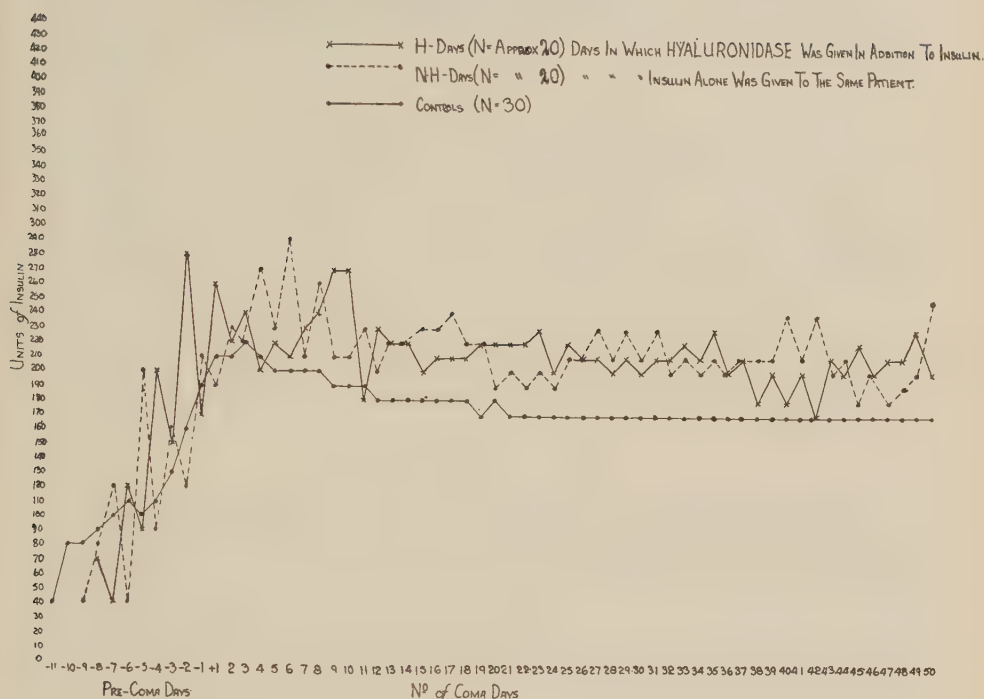


FIG. 1.

## RESTLESSNESS

We are unable to be definite about the effect of hyaluronidase in this respect. The reasons have already been given, i.e. that there are at least three different types of restlessness and each would have to be measured separately; also, there are patients who go into coma smoothly without exhibiting any of the forms, and thirdly, "restlessness" may occur at all stages and would have to be assessed separately for its occurrence and modification by hyaluronidase during the pre-sopor stage, during sopor, coma, and during the waking-up period. The writer is unable to give even an impression concerning restlessness, but two of the nurses in charge of the insulin unit reported that there was no change and one (A.E.) was quite definite that a favourable change took place on hyaluronidase days. He quotes three cases (only one of them in the group of the 32 cases under consideration). Without detailed measurements the report is that the sopor time was shortened by approximately 20 minutes by hyaluronidase and "that during those days there was less restlessness" (43rd=52nd coma). In another case he states that "the patient did not become so distressed after nasal feed and usually woke up more easily". For the third case (second case of group IV) he states that the restlessness changed somewhat in character, as if "the punch had gone out of him". The amplitude of the excursions of the limbs appeared to be somewhat reduced.

In 9 of the 32 patients no restlessness was observed. In 11 cases there was a moderate amount of restlessness present, but no noticeable difference between the H and non-H days. In 12 cases restlessness was marked and measured in minutes (taken as all measurements to the nearest 5 minutes). If one differenti-



TABLE II  
*Clinical Features of 32 Patients*

|      | 1           | 2   | 3                 | 4                                       | 5                | 6                        | 7                                   | 8                              | 9              | 10                      | 11                               |
|------|-------------|-----|-------------------|-----------------------------------------|------------------|--------------------------|-------------------------------------|--------------------------------|----------------|-------------------------|----------------------------------|
|      | Patient No. | Sex | Age<br>(in years) | Duration of<br>Psychosis<br>(in months) | Mode of<br>Onset | Type of<br>Schizophrenia | Weight on<br>Admission<br>(in lbs.) | Gain in<br>Weight<br>(in lbs.) | Body-<br>Build | Previous<br>Personality | Dosage<br>(Average<br>Coma Dose) |
| I:   | +1          | ..  | 28                | 3                                       | S                | H                        | 128                                 | 10                             | L              | AN                      | 340                              |
|      | +2          | ..  | 44                | 1                                       | S                | P                        | 111                                 | 36                             | L              | AN                      | 169                              |
|      | +3          | F   | 32                | 1                                       | S                | P                        | 100                                 | 15                             | L              | SC                      | 246                              |
|      | +4          | M   | 24                | 3                                       | S                | P                        | 184                                 | 21                             | L              | CY                      | 264                              |
|      | 5           | ..  | 33                | 6                                       | S                | P                        | 198                                 | 3                              | L              | SE                      | 178                              |
|      | +6          | M   | 22                | 12                                      | G                | P                        | 121                                 | 20                             | L              | HY                      | 248                              |
|      | 7           | ..  | 36                | 6                                       | S                | P                        | 126                                 | 13                             | L              | SE                      | 256                              |
|      | 8           | ..  | 32                | 36                                      | S                | P                        | 139                                 | 9                              | L              | PS                      | 239                              |
| II:  | +1          | ..  | 30                | 1                                       | S                | H                        | 106                                 | 14                             | A              | CY                      | 299                              |
|      | +2          | F   | 18                | 12                                      | G                | S                        | 124                                 | 22                             | L              | SC                      | 480                              |
|      | +3          | M   | 40                | 1                                       | S                | H                        | 131                                 | 21                             | A              | AN                      | 88                               |
|      | 4           | ..  | 33                | 1                                       | S                | P                        | 112                                 | 13                             | L              | SE                      | 508                              |
|      | +5          | M   | 23                | 4                                       | G                | H                        | 119                                 | 20                             | L              | SC                      | 188                              |
|      | +6          | M   | 18                | 1                                       | S                | P                        | 167                                 | 9                              | L              | AN                      | 214                              |
|      | +7          | ..  | 46                | 8                                       | S                | H                        | 157                                 | 7                              | L              | AN                      | 327                              |
|      | +8          | F   | 25                | 6                                       | G                | P                        | 125                                 | 9                              | L              | SE                      |                                  |
| III: | 1           | ..  | 33                | 1                                       | S                | P                        | 101                                 | 26                             | L              | SE                      | 212                              |
|      | 2           | M   | 28                | 36                                      | G                | P                        | 113                                 | 9                              | L              | SC                      | 192                              |
|      | 3           | M   | 26                | 1                                       | S                | P                        | 129                                 | 11                             | A              | AN                      | 134                              |
|      | 4           | ..  | 37                | 1                                       | S                | P                        | 118                                 | 1                              | L              | AN                      | 200                              |
|      | 5           | F   | 21                | 2                                       | G                | H                        | 122                                 | 17                             | L              | SE                      | 178                              |
|      | 6           | M   | 27                | 24                                      | G                | P                        | 113                                 | 9                              | L              | SC                      | 132                              |
|      | 7           | M   | 29                | 24                                      | G                | P                        | 152                                 | 23                             | A              | SE                      | 301                              |
|      | +8          | M   | 39                | 18                                      | G                | H                        | 125                                 | 17                             | L              | SC                      | 130                              |
| IV:  | 1           | ..  | 36                | 6                                       | G                | P                        | 117                                 | 18                             | A              | SE                      | 218                              |
|      | +2          | M   | 19                | 1                                       | S                | H                        | 137                                 | 6                              | P              | AN                      | 341                              |
|      | 3           | M   | 23                | 3                                       | G                | H                        | 140                                 | 19                             | A              | SC                      | 112                              |
|      | 4           | ..  | 21                | 12                                      | G                | C                        | 109                                 | 17                             | L              | SC                      | 264                              |
|      | +5          | F   | 18                | 1                                       | S                | P                        | 106                                 | 17                             | L              | SE                      | 144                              |
|      | 6           | ..  | 24                | 18                                      | G                | S                        | 163                                 | 22                             | A              | SC                      | 439                              |
|      | 7           | ..  | 24                | 3                                       | G                | H                        | 119                                 | 11                             | A              | SC                      | 317                              |
|      | 8           | M   | 23                | 1                                       | S                | H                        | 148                                 | 15                             | L              | SC                      | 216                              |

## REMARKS

Column 4: Duration of psychosis in months; if "1" this means one month or less, possibly only a few days; 5: Mode of onset; Sudden (over months) = S; Gradual (over months) = G; 6: Type of Schizophrenia (predominant type): H = hebephrenic; S = simple schizophrenia; P = paranoid; C = catatonia; 9: Body-build; A = athletic; L = leptosome asthenic; 10: Previous personality; PS = psychopathic; SC = schizoid; AN = anankastic; SE = sensitive; CY = cyclofyme; HY = hysterical. + before the patients number = statistically significant changes occurred during hyaluronidase days in one or several respects.

ates between (1) excessive twitching in pre-sopor and early sopor, (2) writhing movements, contortions and hyper-extension in sopor, (3) hyper-extension and whole body contortions in coma and (4) contortions, hyper-extension spasm and writhing movements during the waking time, the following table gives some indication of the distribution.

| Patient<br>Type of | I/2 | I/4   | I/5 | I/6 | I/8 | II/2 | II/7    | III/1 | III/3 | III/4 | III/7 | IV/2      |
|--------------------|-----|-------|-----|-----|-----|------|---------|-------|-------|-------|-------|-----------|
| Restlessness       | 2/3 | 1 1/3 | 1   | 2   | 2   | 2    | 1 1/2/3 | 1     | 3     | 2     | 2/3/4 | 1 1/2/3/4 |

In patient I/6 a diminution of the duration of restlessness occurred by two minutes (average), patient II/7 however, was "if anything a little worse during the H days". In patient III/3 the amount of respiratory distress which soon set in after the onset of coma (only allowing for comata of 5 minutes duration), was unchanged under hyaluronidase medication. The favourable effect of hyaluronidase in patient IV/2 has already been mentioned above. In the remainder of the patients the final comment has always been: "no difference as to duration and intensity of the various forms of restlessness."

#### CLINICAL CORRELATIONS

We will now try to answer the question whether relationships can be established between (a) those cases in which hyaluronidase produced very definite favourable changes and (b) features which these patients might otherwise share; e.g. 1. Sex. 2. Age. 3. Duration of psychosis. 4. Mode of onset. 5. Type of psychosis. 6. Weight on admission. 7. Gain in weight, during the insulin course. 8. Body build. 9. Pre-psychotic personality. 10. Average coma dosage of insulin required. These features are given in Table III. No attempt is made to interpret them but they are worth recording in case of future research. The table lists only those features which are significantly changed during the days of hyaluronidase addition to the insulin dosage.

#### DISCUSSION AND CONCLUSION

The results of the current investigation are somewhat at variance with other reports. We have tried to cover as many as possible of the aspects mentioned in other papers. Several factors have been assessed which were not considered previously, e.g. "Stability of onset" and the number of epileptiform fits. A curious feature is our generally rather high dosage as compared with other (especially French) workers. Possibly the increase of the dosage by 40 units daily until coma is produced rather than increases by 10 units daily may explain this difference, together with the differences in coma time lag and our method of arriving at the "average coma dose". Unfortunately in the other papers, body weights are not quoted so that comparison in this direction is not possible.

In the preceding results the statistical comments concerning patients of the "Pilot group" should be considered in the light of the limited number of days involved.

Whilst it appears that the addition of hyaluronidase does influence some of the events during the insulin coma treatment of schizophrenia and mostly in a favourable direction, we are unable to confirm the extensive changes claimed by other authors. Our results indicate that definite clear-cut changes only occur in a few patients, and there is a suggestion that these affected features occur in the acute hebephrenic group. A further trial of hyaluronidase in certain "difficult cases" appears worth while. Data are given to help selection of these cases (Table III). Restlessness, whilst possibly being qualitatively influenced, warrants

TABLE III  
Common Features Shared by Patients Who are Significantly Affected in One Factor by Hyaluronidase

| 1                                | 2                           | 3      | 4                 | 5                                          | 6                | 7                             | 8                                   | 9                              | 10             | 11                                             | 12                              |
|----------------------------------|-----------------------------|--------|-------------------|--------------------------------------------|------------------|-------------------------------|-------------------------------------|--------------------------------|----------------|------------------------------------------------|---------------------------------|
| Factor                           | Patient                     | Sex    | Age<br>(in years) | Duration<br>of<br>Psychosis<br>(in months) | Mode of<br>Onset | Type of<br>Schizo-<br>phrenia | Weight on<br>Admission<br>(in lbs.) | Gain in<br>Weight<br>(in lbs.) | Body-<br>Build | Previous<br>Personality                        | Dosage<br>(average<br>per coma) |
| Sopor<br>duration                | II/5<br>II/8                | M<br>M |                   |                                            | G<br>G           | H<br>H                        | 130<br>125                          | 20<br>17                       | L<br>L         | Schizoid<br>Schizoid                           |                                 |
| Onset of<br>coma                 | I/3<br>II/1                 | F<br>F | 32<br>30          | 1<br>1                                     | S<br>S           | H<br>H                        | 100<br>106                          | 15<br>14                       |                |                                                |                                 |
| Stability<br>of onset<br>of coma | I/1<br>II/1<br>II/3<br>IV/2 |        |                   | 3<br>1<br>1<br>1                           | S<br>S<br>S<br>S | H<br>H<br>H<br>H              | 128<br>106<br>131<br>137            |                                |                | Anankast<br>Cyclothyme<br>Anankast<br>Anankast | 340<br>299<br>88<br>341         |
| Waking<br>duration               | II/7<br>IV/5                |        |                   |                                            | S<br>S           | P<br>P                        |                                     |                                |                |                                                |                                 |

Symbols employed in this table as in Table II.



SAMPLE OF RECORDINGS (Condensed from Daily Sheets). Patient II/2.

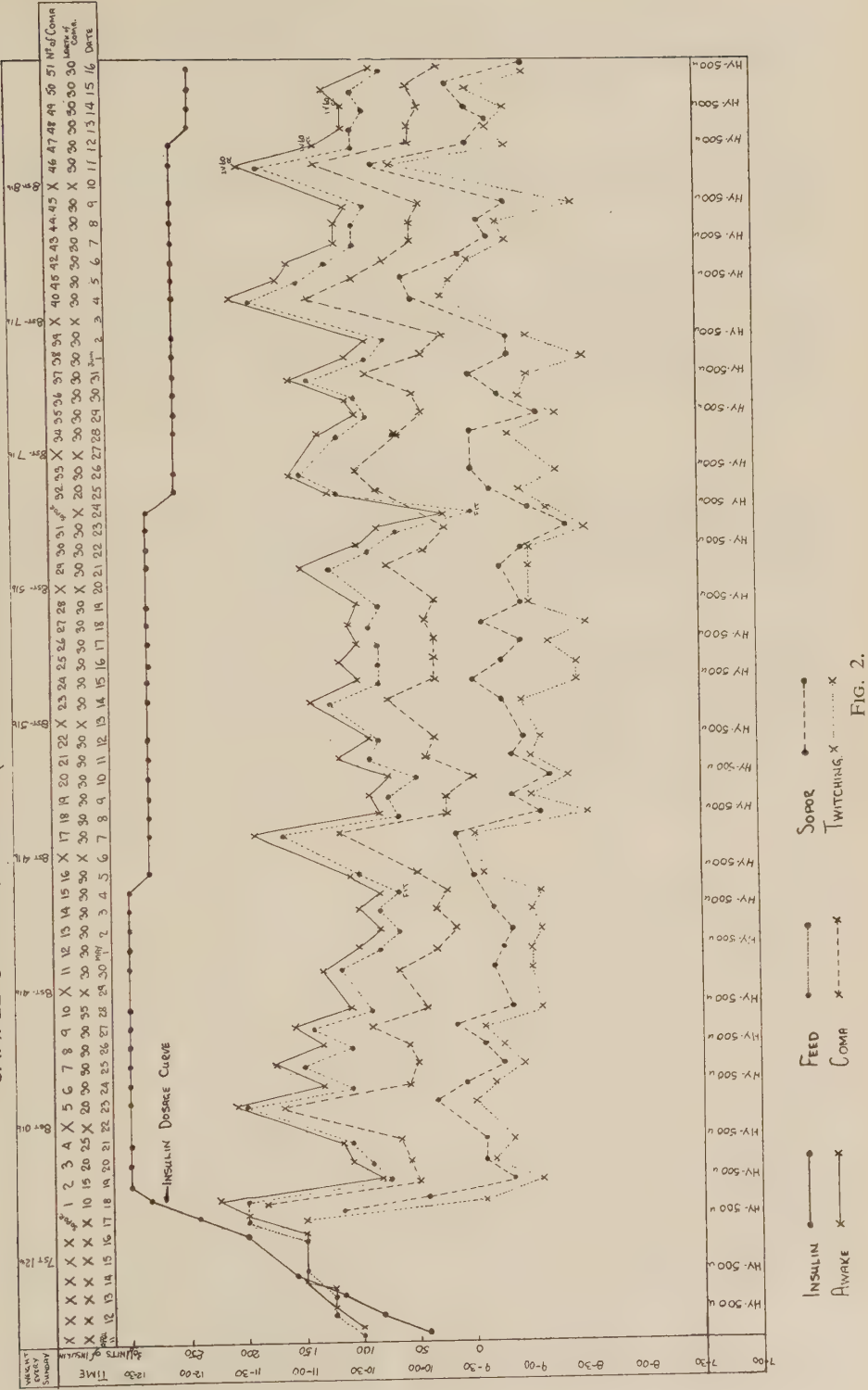


FIG. 2.

a special study with precise measurements and definitions. With the criteria set in *this* trial for the reduction of insulin dosage, no such reduction appeared indicated or possible by the addition of hyaluronidase to the insulin injected.

#### SUMMARY

A trial has been carried out on 32 schizophrenic patients receiving courses of insulin coma treatment to determine by measurements, whether the various stages of the coma could be favourably influenced by the addition of hyaluronidase to the insulin dosage. The patients were divided into four groups of 8 patients each, who received the hyaluronidase (apart from a pilot-group) on alternate days, alternate weeks, and from the 16th to the 30th coma respectively.

The factors assessed were duration of sopor, onset of coma, stability of onset of coma, waking duration, necessity for intravenous glucose interruption, epileptiform fits, after-shocks and insulin dosage. Most of the factors appeared significantly favourably influenced by the addition of hyaluronidase in a few patients only, except for dosage where no drastic reduction appeared to be indicated or possible in any single case with the criteria adopted.

An attempt is made to correlate these data with characteristics of the patients and the features of their psychosis. The results indicate the possible importance of the acute hebephrenic group.

#### ACKNOWLEDGMENTS

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# BODY FLUID INDOLES OF NORMAL AND MENTALLY-ILL SUBJECTS

## I. PRELIMINARY SURVEY OF THE OCCURRENCE OF SOME URINARY INDOLES

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A ROLE in mental illness for an aberrant metabolism of indole compounds was first advanced some sixty years ago, when their alleged toxicity to the nervous system figured prominently in the then current theory of auto-intoxication by bacterial action in the bowel (Herter, 1898, 1907). Although in a modified form it continues to receive the support of Buscaino (1958), auto-intoxication of this nature is now generally rejected as a factor in mental illness (see particularly Alvarez, 1924) and the renewed interest in indoles and brain function of recent years has come from a different standpoint. Thus, study of the central nervous system effects of indoles such as 5-hydroxytryptamine (serotonin) and bufotenin, and of compounds containing an indole group such as lysergic acid and reserpine, has inspired several new theories concerning normal and abnormal roles for indoles in the brain (Woolley and Shaw, 1957; Brodie and Shore, 1957; Hoffer, 1957).

Reports of body fluid abnormalities involving indoles in groups of mentally-ill subjects have occasionally appeared in the literature. Many of the earlier papers are listed and briefly reviewed by McGeer, McNair, McGeer and Gibson (1957). In our opinion it is difficult to assess the significance of most of these studies, as the methods used were usually relatively non-specific for indoles and the experiments often inadequately controlled, but the general impression emerges that indoles may be concerned in the increased concentration of aromatic compounds often observed in the urine of acutely disturbed patients, particularly schizophrenics. Well-defined disturbances of indole metabolism, however, have been found in two rare hereditary conditions exhibiting mental abnormalities: in phenylketonuria (Armstrong and Robinson, 1954; Pare, Sandler and Stacey, 1957) and in the pellagra-like syndrome known as Hartnup disease (Baron, Dent, Harris, Hart and Jepson, 1956; Rodnight and McIlwain, 1955; Jepson, 1956; Hersov and Rodnight, in preparation); and also in a group of schizophrenics, who were found by Zeller, Bernsohn, Inskip and Lauer (1957) to metabolize large doses of tryptophan differently from normal subjects.

It is clear, therefore, that much scope exists for further work in the subject. In the research now described aspects of body fluid indoles have been studied and compared in normal and mentally-ill subjects by chromatographic methods. The present paper, which is in the nature of a preliminary survey, reports on



the occurrence of the main urinary indoles in 156 mental hospital patients, 63 normal subjects and 35 general hospital patients. Subsequent papers will be concerned with the urinary excretion in mental disease of serotonin, tryptamine and some indole acids, and observations on indoles in blood.

### SUBJECTS

The 254 subjects were divided into the 5 groups described below. Details of their sex and age are given in Table I. About three-quarters of the mentally-ill subjects were receiving some form of treatment, mainly electro-shock therapy,

TABLE I  
*Classification of Subjects: Sex and Age*

| Classification of Subjects by Sex and Age |                                        |        |     |             |         |     | Number<br>Examined | Age in Years Followed<br>by S.D. and Range |  |
|-------------------------------------------|----------------------------------------|--------|-----|-------------|---------|-----|--------------------|--------------------------------------------|--|
| Group                                     | Description                            |        |     |             |         | Sex |                    |                                            |  |
| I                                         | Normals .. .. .                        | Male   | 37  | 33.1 ± 9.4  | (19-61) |     |                    |                                            |  |
|                                           |                                        | Female | 26  | 30.6 ± 10.6 | (18-52) |     |                    |                                            |  |
| II                                        | Schizophrenics in hospital .. .        | Male   | 27  | 34.0 ± 9.6  | (22-56) |     |                    |                                            |  |
|                                           |                                        | Female | 38  | 33.1 ± 10.8 | (18-61) |     |                    |                                            |  |
| III                                       | Other mental illnesses in hospital ..  | Male   | 20  | 55.1 ± 12.3 | (30-71) |     |                    |                                            |  |
|                                           |                                        | Female | 40  | 49.2 ± 14.3 | (16-69) |     |                    |                                            |  |
| IV                                        | New admissions to Observation Ward     | Male   | 17  | 34.4 ± 8.6  | (22-53) |     |                    |                                            |  |
|                                           |                                        | Female | 14  | 40.1 ± 13.0 | (22-60) |     |                    |                                            |  |
| V                                         | Physical illnesses in General Hospital | Male   | 19  | 46.5 ± 18.6 | (15-79) |     |                    |                                            |  |
|                                           |                                        | Female | 16  | 36.9 ± 18.9 | (13-67) |     |                    |                                            |  |
| Total .. .. .                             |                                        |        | 254 |             |         |     |                    |                                            |  |

or sedation with chlorpromazine or barbiturates. Treatment was not suspended before collection of the specimens, but a record of its nature was kept for each patient.

*Group I.* A total of 63 healthy normal subjects from the staff of a mental hospital and their friends and relatives volunteered specimens. No special dietary instructions were given.

*Group II.* This group comprised 65 patients suffering from schizophrenia and drawn from three distinct mental hospital populations. All of them had been detained in hospital for longer than three weeks.

*Group III.* Miscellaneous mental illnesses other than schizophrenia formed this group. A total of 60 patients were chosen from the same three mental hospitals as was the case with Group II subjects, and are roughly classified as follows: 20 depressive illnesses, 17 involutional and senile states including organic illnesses, 7 manic psychoses, 5 cases of psychoneurosis, 3 epileptics and 3 psychopaths.

*Group IV.* Acutely-ill subjects were obtained from amongst new admissions to the psychiatric observation ward of a general hospital. There were 31 subjects; the provisional diagnosis of 25 of them was schizophrenia; for the remainder it was depression or hypomania.

*Group V.* The final group consisted of 35 patients with physical illnesses drawn from a different general medical hospital to the one referred to above. They comprised 7 patients from whom the specimen was obtained 1-3 days

after a major operation, 6 cardiovascular diseases, 6 patients with neoplasms, 6 endocrine disorders, 4 toxæmias from various causes, 4 inflammatory conditions and 2 blood diseases.

#### METHODS

*Specimens.* Urine was collected before breakfast in glass or polythene containers without the addition of preservative. The great majority of specimens were analysed on the day of their collection in batches of 12 or more; in a few instances where immediate analysis was not possible they were stored at  $-20^{\circ}\text{C}$ .

*Chromatography.* The method employed was similar in principle to that described by Jepson (1955). The urine spot was placed 5.5 cm. along the diagonal of a 9 cm. square sheet of Whatman No. 20 chromatography paper having holes punched in each corner. The use of Whatman No. 20 paper is an important technical detail, as unsatisfactory results were obtained with faster running papers such as Whatman No. 1. To apply the spot an "Agla" micro-meter syringe (Messrs. Burroughs Wellcome Ltd.) was used: the syringe was clamped so that the needle just touched the paper, the urine added in 5  $\mu\text{l}$ . portions and after each addition the spot was dried with air at  $40^{\circ}\text{C}$ . from an electric blower. The maximum volume of urine commensurate with the production of undistorted chromatograms was applied. With practice its approach could be judged firstly by the rate at which each successive 5  $\mu\text{l}$ . of urine soaked into the paper, and secondly by the appearance of the dried spot, whose circumference became crinkly and distorted when the critical volume was reached. The volume of urine used with each specimen was noted and the mean value calculated for each group (Table II).

TABLE II  
*Mean Volume of Urine used for Chromatography in each Group*  
Mean Volume in  $\mu\text{l}$ .

| Group               | I     | II    | III   | IV    | V     |
|---------------------|-------|-------|-------|-------|-------|
| First specimens ..  | 95.5  | 96.3  | 97.4  | 110.0 | 108.0 |
| Second specimens .. | 104.3 | 106.1 | 101.6 | —     | —     |

The paper squares were fitted on to a chromatography frame of the same basic design as that described by Datta, Dent and Harris (1950), but constructed from  $\frac{1}{8}$  inch diameter stainless steel rod and  $\frac{1}{4}$  inch thick sheet polythene, instead of aluminium alloy. Short lengths of glass tubing were used as spacing washers. The frame, which accommodated 12 papers, was placed in a polythene tray containing the first solvent, which in turn rested in a glass tank of dimensions  $16 \times 11 \times 11$  inches, and covered with a sheet of glass.

The papers were first irrigated overnight with a n-propanol/water ammonia mixture of proportions 80:15:5, and the next day for 6 hours with the n-butanol/acetic acid/water solvent of Jepson (1955). Before developing the indole spots with Ehrlich's reagent, the dried papers were viewed in ultra-violet light and the fluorescent spots outlined in pencil.

Indoles and other compounds reacting with *p*-dimethylamino-benzaldehyde were located with the Ehrlich reagent of Jepson (1955). The papers were dipped in the reagent and examined at intervals of 5 minutes for about 20 minutes and again after 24 hours. The blue and purple spots of the indoles were marked with pencil as they appeared; several of the fainter spots faded rapidly.

According to their maximum intensity they were given a rating of faint, weak, medium or strong. By examining in a few instances a series of dilutions of the same urine the quantitative relation between the faint to weak and the weak to medium ratings was very roughly estimated as twofold.

The reproducibility of the method from day to day was high: on repeatedly analysing a single specimen, the same spots were noted with the same rating. However, it was considered inevitable that over a period of months minor variations would occur in the conditions under which the chromatography was carried on. To reduce the effect of these, abnormal specimens were usually analysed in parallel with some normal specimens collected during the same period. Nearly all of the specimens from Groups I to III, about three-quarters of those from Group IV and one-third from Group V, were dealt with in this way.

*Comment on Method of Preparing Chromatograms.* The early morning specimens varied considerably in concentration and in preparing the chromatograms it clearly would have been unsatisfactory to use a standard volume of urine. The method described above of applying to the paper the maximum volume of urine was found to compensate approximately for differences in urinary concentration, since the required volume was roughly inversely proportional to the specific gravity. The procedure was further investigated as follows: from a random selection of 16 urines, spots were prepared on tarred squares of paper. These were dried in a vacuum desiccator, weighed, and the weight of the urinary solutes deposited determined in each case. The mean weight was  $4.46 \pm 0.92$  mg. (standard deviation) and the mean volume applied was  $105 \pm 33$   $\mu$ l.; the correlation coefficient of the two sets of figures was  $-0.2$ , revealing no tendency for the urinary concentration to influence the quantity of urinary solutes deposited on the paper.

## RESULTS

### *Pattern of Indole Spots in Normal Subjects*

The indoles were identified by their position on the chromatograms relative to themselves, to the fluorescent spots of other compounds and to the large urea spot which was coloured yellow by the Ehrlich reagent. The approximate positions occupied by the indoles are illustrated in Figure 1. Further clues as to their identity were given by the characteristics of their reaction with Ehrlich's reagent, details of which are given in Table III.

TABLE III

*Details of Indole Spots Observed on Chromatograms of Normal Urine Specimens*

| Description of Spot        | Colour with Ehrlich's Reagent | Approximate Time for Appearance of Weak Spot (minutes) |
|----------------------------|-------------------------------|--------------------------------------------------------|
| Indican .. .. .            | Brown                         | 3                                                      |
| Tryptophan .. .. .         | Purple                        | 4                                                      |
| Indole acetic acid .. .. . | Red-purple                    | 3                                                      |
| "Unknown 1" .. .. .        | Red-purple                    | 5                                                      |
| "Unknown 2" .. .. .        | Purple to blue                | 1 or less                                              |
| "Unknown 3" .. .. .        | Blue-purple to blue           | 6                                                      |
| "Unknown 4" .. .. .        | Red-purple                    | 3                                                      |
| "Unknown 5" .. .. .        | Purple                        | 3                                                      |



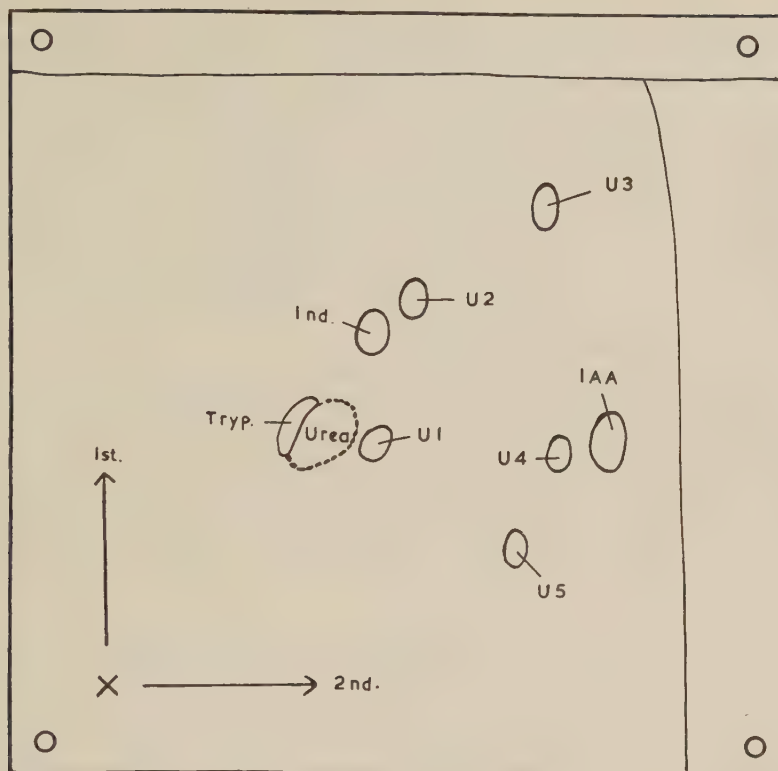


FIG. 1.—Diagram of two-dimensional chromatogram of 100  $\mu$ l. urine, stained with *p*-dimethylaminobenzaldehyde (Ehrlich's reagent) and showing all the observed blue and purple spots and the yellow spot of urea. 1st solvent: *n*-propanol/water/ammonia, 80:15:5; 2nd solvent: *n*-butanol/acetic acid/water (Jepson, 1955). "Tryp.": Tryptophan; "Ind.": Indican; "I.A.A.": Indole acetic acid; "U 1-5": Unknowns 1-5.

From the Figure and Table III it can be seen that the indican spot was clearly differentiated from the other indoles by its distinctive brown colour. Two other spots were identified with reasonable certainty as tryptophan (purple) and indole acetic acid (red-purple). Faint spots of tryptophan were readily masked by the yellow colour of the closely adjacent urea. The remaining 5 blue or purple spots could not be definitely recognized as known indoles, although in some cases their identity was suspected. The only chemical evidence for their indolic nature is the colour they gave with Ehrlich's reagent, which is not known generally to produce blue or purple hues with other classes of compounds. They are referred to as "unknowns 1-5"; some of their properties and suggestions for their identity are given below.

"Unknown 1". This spot very probably corresponds to indole acetyl glutamine, a compound found in much higher concentration in urine from cases of Hartnup syndrome (Jepson, 1956). An authentic specimen for comparison was not available, but the chromatographic behaviour of the spot in several solvent systems was identical with the indole acetyl glutamine spot in urine from a known case of Hartnup disease.

"Unknown 2". The spot reacted very rapidly with the Ehrlich reagent, the colour often appearing immediately on dipping the paper. The initial colour was purple, turning within 15-30 minutes to a pure cobalt blue, which

with strong spots was permanent for weeks. The substance was not extracted from salt-saturated urine by benzene or ether at either acid or alkaline pH's, but was partially extracted by n-butanol after saturation of the urine with potassium carbonate. On paper it gave no colour with ninhydrin, diazotized sulphanilic acid or ammoniacal silver nitrate. In  $R_f$  and reaction to Ehrlich's reagent it is very similar to the unknown spot No. 2 described in urine extracts by Decker (1954), who considers it a derivative of skatol. We have confirmed that this is indeed likely by feeding skatol to rats and observing a great increase in the amount of "unknown 2" in the urine; other new indoles also appeared. We were not, however, able to demonstrate on the present spot, either in human urine or in rat urine after feeding skatol, the "fluorindal" reaction, typical according to Decker (1955) of his substance.

"Unknown 3", also gave a spot initially purple, changing to a semi-permanent grey-blue colour, but it developed more slowly than was the case with "unknown 2". It gave no reaction to reagents other than Ehrlich's and was apparently acidic in character since, from salt-saturated urine at pH 2, it was completely extracted by n-butanol and partially extracted by ether. Its position on the chromatogram was very close to that occupied by tryptamine. The latter, however, is definitely excluded as it only occurs in urine in quantities of the order of 0.1  $\mu\text{g./ml.}$  and requires for its demonstration special methods (Rodnight, 1956).

"Unknown 4 and 5" were less frequently seen and then only as faint spots. They probably correspond to the compounds indole lactic acid and 5-hydroxy-indole acetic acid respectively. Thus both were quantitatively extracted from salt-saturated urine at pH 2 by ether and on chromatograms of the ether extract they gave identity with authentic samples of the two indole acids.

### *Pattern of Indole Spots in Abnormal Subjects*

Chromatograms of the abnormal urines showed no blue or purple spots other than those noted in normal specimens and described above.

The frequencies with which the normal spots occurred, expressed as percentages of the number of subjects in each group, are given in Table IV.

TABLE IV  
*Frequency of Occurrence of Indole Spots on Chromatograms*

Results are quoted as percentages of the total number of subjects in the group; those which differ significantly from the normal (Group I) percentage are marked with an asterisk ( $P < 0.01$ ). I: 63 normal subjects, II: 65 schizophrenics, III: 60 miscellaneous mental illnesses, IV: 31 new admissions to a psychiatric observation ward (mainly schizophrenics), V: 35 physical illnesses from a general hospital. For further details see text.

| Description of Spot                 | No Spot (%) |     |       |       |       | Low Intensity Spot (%) |       |       |       |       | High Intensity Spot (%) |       |     |     |    |
|-------------------------------------|-------------|-----|-------|-------|-------|------------------------|-------|-------|-------|-------|-------------------------|-------|-----|-----|----|
|                                     | I           | II  | III   | IV    | V     | I                      | II    | III   | IV    | V     | I                       | II    | III | IV  | V  |
| Indican ..                          | 0           | 0   | 2     | 0     | 0     | 73                     | 46(*) | 67    | 52    | 80    | 27                      | 54(*) | 31  | 48  | 20 |
| Tryptophan ..                       | 19          | 27  | 28    | 19    | 14    | 73                     | 62    | 60    | 81    | 69    | 8                       | 11    | 12  | 0   | 17 |
| Indole acetic acid ..               | 8           | 9   | 17    | 6     | 14    | 86                     | 83    | 78    | 77    | 83    | 6                       | 8     | 5   | 17  | 3  |
| "Unknown 1" ..                      | 24          | 35  | 50(*) | 61(*) | 77(*) | 74                     | 62    | 50(*) | 36(*) | 23(*) | 2                       | 3     | 0   | 3   | 0  |
| "Unknown 2" ..                      | 64          | 55  | 46    | 29*   | 74    | 27                     | 26    | 28    | 32    | 23    | 9                       | 19    | 26  | 39* | 3  |
| "Unknown 3" ..                      | 34          | 51  | 45    | 42    | 71*   | 63                     | 43    | 52    | 55    | 23*   | 3                       | 6     | 3   | 3   | 6  |
| "Unknown 4" ..                      | 98          | 94  | 88    | 90    | 92    | 2                      | 6     | 12    | 10    | 8     | 0                       | 0     | 0   | 0   | 0  |
| "Unknown 5" ..                      | 83          | 59* | 73    | 74    | 89    | 17                     | 38*   | 25    | 23    | 11    | 0                       | 3     | 2   | 2   | 0  |
| Total spots<br>(of possible 800) .. | 330         | 330 | 349   | 321   | 431   | 415                    | 366   | 372   | 366   | 320   | 55                      | 104   | 79  | 113 | 49 |

Here it was found more satisfactory to condense the five ratings of spot intensity to three by combining the faint and weak spots and the medium and strong spots into low and high intensity ratings respectively. The condensation was probably necessary because the subjective error involved in judging the spot

intensities was too great to allow more than two levels to be used in groups of the present size; other groupings of the original ratings gave no more information.

In order to determine the reliability of observed differences of frequency between the groups, it was necessary to obtain a measure of the degree to which the indole excretion pattern was reproducible. Ideally this would be done by examining a series of specimens from each subject, but in practice this course was not possible. An approximate estimate of overall reproducibility was accordingly made by analysing a second specimen of urine, one to three weeks after the first, from just over one-third of the subjects in Groups I-III. With one exception the resulting percentages agreed with those from the first specimens to within 20 per cent. To estimate reproducibility in individual subjects, the results from the second specimens were combined with those from the corresponding first specimens and the percentage frequency for each spot re-calculated; for convenience this is referred to as the "combined percentage". The upper and lower limits of the "combined percentage" were obtained by comparing each pair of specimens, scoring the discordant results as agreements in each direction and then re-calculating the percentage. These data are given in Table V, where it can be seen that reproducibility is highest

TABLE V

*Frequency of Occurrence of Indoles in Combined Groups of First and Second Specimens*

| Description of Spot   | No Spot (%) |       |       | Low Intensity Spot (%) |       |       | High Intensity Spot (%) |       |       |
|-----------------------|-------------|-------|-------|------------------------|-------|-------|-------------------------|-------|-------|
|                       | I           | II    | III   | I                      | II    | III   | I                       | II    | III   |
| Indican ..            | 0           | 0     | 0     | 79±17                  | 63±21 | 63±17 | 21±17                   | 37±21 | 37±17 |
| Tryptophan ..         | 14±10       | 15±4  | 25±25 | 79±12                  | 75±10 | 65±27 | 7±2                     | 10±6  | 10±10 |
| Indole acetic acid .. | 14±7        | 10±10 | 15±10 | 72±9                   | 90±10 | 81±15 | 14±9                    | 0     | 4±4   |
| "Unknown 1" ..        | 19±14       | 19±12 | 33±17 | 81±14                  | 79±13 | 65±19 | 0                       | 2±2   | 2±2   |
| "Unknown 2" ..        | 67±14       | 56±17 | 54±8  | 24±14                  | 21±21 | 29±13 | 9±5                     | 23±12 | 17±8  |
| "Unknown 3" ..        | 36±17       | 58±15 | 65±19 | 64±17                  | 42±15 | 35±19 | 0                       | 0     | 0     |
| "Unknown 4" ..        | 100         | 87±13 | 73±23 | 0                      | 13±13 | 27±23 | 0                       | 0     | 0     |
| "Unknown 5" ..        | 93±7        | 54±19 | 71±17 | 7±7                    | 46±19 | 27±19 | 0                       | 0     | 2±2   |

I: 21 pairs of specimens from subjects in Group I. II: 26 pairs from Group II. III: 24 pairs from Group III. For method of calculating the limits of the percentages see text.

in the normal group. For the abnormal groups it is considerably lower and for some spots it is very low indeed. This is possibly due to the fact that the two specimens may have been collected during different phases of the subjects' illnesses; it may also reflect a higher incidence of somatic disorders in patients than normals, and for Group III subjects a higher average age.

In interpreting the main group differences, significance was first calculated in each case by a "t" test on the standard error of the difference between the percentages observed in the normal and abnormal groups. A strict test of significance was employed; only differences with a level of probability of chance less than 0.01 were accepted. These are marked with an asterisk in Table IV or with an asterisk in parentheses where a significant result was considered unreliable for special reasons stated below. The significant results were then assessed on their individual merits, where possible taking into account the results of the second specimens.

*Indican.* A significantly raised percentage of high intensity spots occurred from Group II subjects. Although the same tendency is evident in the "combined percentages" (Table V), the degree of reproducibility for Group II indican spots is very low and for this reason the result was not accepted as reliably significant.



"*Unknown 1*". Significantly fewer spots of low intensity occurred in Groups III, IV and V, and in the case of Group III a difference in the same direction is present in the "combined percentages". The reliability of this result is also in doubt, because the "unknown 1" spot, which more often than not was classed as faint rather than weak on the original intensity scale, was frequently partially obscured by the yellow colour of the closely adjacent urea. The difference, moreover, was not confined to mentally-ill subjects, but also occurred in the physically-ill subjects of Group V.

"*Unknown 2*". The three groups of mentally-ill subjects all showed an increased percentage of high intensity spots of this substance, although only in Group IV was the difference significant. It is noteworthy that the increase is only evident at the high intensity level; there is little variation in the percentage of low intensity spots occurring. The "combined percentages" from subjects in Groups II and III also gave a result in the same direction.

The significant percentage occurred in Group IV subjects and this suggested that a correlation might be found between its occurrence and the acuteness of the illness. In Group II, 39 of the subjects were acutely disturbed at the time the specimens were obtained. Out of these, 9 or 23 per cent. of the specimens showed a high intensity "unknown 2" spot; in the remaining 26 more chronic patients the figures were 3 or 12 per cent. Although the figure for the acutely-ill subjects is higher it is still not significantly different from the normal value of 9 per cent. (Table IV,  $P \approx 0.1$ ). In the heterogeneous Group III a correlation with diagnosis was sought. Here 16 high intensity "unknown 2" spots were observed; 13 of these occurred in patients with a diagnosis of depression (including 2 involutional melancholias), 2 in cases of senile dementia and one in a patient with psychoneurosis (chronic anxiety). Together with the involutional melancholias the depressive illnesses in the Group totalled 27; amongst these therefore the percentage of strong reactors for "unknown 2" was a significant 48, whilst for the rest of the Group it equalled the normal percentage of 9.

"*Unknown 3*". No explanation is offered for the significantly lower percentage of this spot noted in Group V subjects. Its absence could not be correlated with diagnosis.

"*Unknown 5*". The significantly raised percentage of weak spots in Group II subjects and a trend in the same direction in Groups III and IV, is well reflected in the "combined percentages". There appears therefore no reason to doubt its reliability.

"*Total indole spots*." The individual percentages were totalled for each Group for the main investigation (Table IV). The differences are not significant, but it is noteworthy that the three groups of mentally-ill subjects all show an increase in the percentage of high intensity spots.

## DISCUSSION

### *Experimental Factors*

In planning the present investigation it was considered desirable to examine a wide spectrum of mental illnesses in subjects living under several different hospital regimes. For this reason, and also because the number of subjects was large, it was impossible to control strictly all the experimental variables. The most pertinent of these would appear to be the following:

*Diet:* No control or records were practicable, but by analysing early morning specimens the influence of diet was reduced to the minimum possible without control. Thus the great majority of the subjects had eaten their last meal some 12 hours before the time of the early morning urine collection.

*Drugs and treatment:* About three-quarters of the subjects in Groups II and III were receiving treatment in the form of electro-convulsive therapy, chlorpromazine or barbiturates at the time the specimens were obtained. No significant correlation between treatment and the occurrence of any of the indole spots was found, but there was a tendency for more high intensity spots of "unknown 2" to occur in untreated than in treated subjects; the respective values were 28 per cent. and 17 per cent. *Urinary concentration:* As was mentioned in the Methods section, variations in this were largely compensated for by the procedure for preparing the chromatograms, where the volume of urine was roughly inversely proportional to its specific gravity. However, it is possible that the method would have been adequate if the mean specific gravities varied greatly between the groups; in fact this did not occur, since the mean volumes of urine used in each group agreed closely (Table II). *Fluctuations in level of indole excretion:* The degree to which indole excretion varies from hour to hour is not known. In theory, such short term fluctuations could have been allowed for by pooling all the urine passed over a period of time (e.g. 24 hours), but in practice this was not possible. Some reliance may be placed on the fact that the specimens were obtained from all the subjects at the same time of day, and at rest.

In the absence of experiments in which the above factors were standardized, it is not possible to determine precisely their influence on the present results. It seems very unlikely, however, that the significant differences can be wholly ascribed to chance variations in the experiments circumstances. This is concluded because (a) the total number of subjects was relatively large, (b) a strict test of significance ( $P < 0.01$ ) was applied to the results, (c) the specimens were obtained from virtually fasting subjects in the early morning and (d) in a proportion of subjects the significant difference was approximately confirmed by analyses of second specimens.

### *Pattern of Indole Spots*

The most interesting result concerned the substance labelled "unknown 2", in which a significantly raised percentage of high intensity spots were observed in urines from acutely-ill new admissions to a psychiatric observation ward, and in urines from nearly half the depressed patients detained in hospital. Results from the schizophrenic subjects were suggestive, although not statistically significant, of an increase in acutely-ill patients. However, a raised excretion of the substance was not confined to the mentally-ill subjects, since in a few normal subjects high intensity spots were also noted. No correlation between age or sex and the occurrence of high intensity spots of "unknown 2" was found.

The substance appears to be derived from skatole, which in turn almost certainly arises from the action of bacteria on tryptophan in the intestine. Probably, as Decker (1955) suggests, it represents a product of the detoxication of skatol by the liver, as does indican of indole. It would be particularly interesting to know whether the excretion of the substance varies from day to day, or whether it is relatively constant and thus part of the concept of biochemical individuality, as has been observed for amino acids (Dent, 1954;

Williams, 1956). In the event of the former it could be postulated that excretion is influenced by factors such as digestion or bowel function, which are occasionally disturbed in normal subjects and more often so in the mentally ill. A persistently raised excretion, on the other hand, would require a different interpretation; it is tempting to suggest that it might prove a metabolic pointer to a higher than normal susceptibility to certain forms of mental illness, just as recent work has shown that a persistently raised level of indican in the urine may indicate a susceptibility to the pellagra-like attacks observed in Hartnup disease (Rodnight and McIlwain, 1955; Jepson, 1956; Hersov and Rodnight, in preparation). Evidence for this cannot be derived from the chronically-ill subjects of the present investigation (who differed little from normal in their excretion of the substance), since they were drawn from a different population to the acutely-ill subjects. Longitudinal studies with a fully quantitative method on patients and normals showing a raised excretion are required.

Stress, using the term in its widest and non-specific sense, does not appear to influence the excretion of "unknown 2", since the lowest percentage of high intensity spots of all was found in the physically-ill patients from a general hospital, including some examined very soon after a major operation.

A further significant difference was found for "unknown 5", where more low intensity spots were observed in schizophrenic subjects. Since this spot is believed to be 5-hydroxyindole acetic acid and is the subject of a quantitative study in a later paper, discussion of the result will be deferred until then. Buscaino and Stefanachi (1957) and Sano (1957) were unable to find any abnormality in the urinary excretion of 5-hydroxyindole acetic acid in schizophrenia.

The absence of a reliably significant difference in the percentage of indican spots observed is in accord with the early, but excellent, study of Borden (1906), who measured by a quantitative adaptation of the Obermayer reaction the 24-hourly output of indican in normal and mentally-ill subjects. He found widely varying values in both groups, but little difference in the mean daily excretion. It would seem, therefore, that a moderate degree of indicanuria is of no significance in mental illness, and the occasional reports which have appeared contradicting this conclusion (Townsend, 1905; Gullotta, 1929; Sano, 1954) are probably explained by the use of relatively non-specific methods and the influence of diet, which is known to affect indican excretion (Borden, 1906; Underhill and Simpson, 1920). As has already been mentioned a persistently high level of indican in the urine may indicate Hartnup disease; none of the high intensity spots observed in the present study approached the intensity of the indican spot in a typical Hartnup urine.

#### *Absence of Abnormal Indoles*

Although no evidence emerges from the present work for the occurrence in the urine of mentally-ill subjects of an "indole toxin", it is necessary to point out that an abnormal indole excretion of less than about 10 mg./24 hours, would not have been detected by the method used. That such an excretion might be important is clear when one considers the potency for the nervous system of indole-containing alkaloids like lysergic acid diethylamide and reserpine which are effective in man in doses of 100  $\mu$ g. and 5 mg. respectively.

Support, however, for the present negative result comes from the work of Curzon (1957), who studied indole excretion by paper chromatography in schizophrenic and non-schizophrenic (mainly neurotic) mental hospital patients,



and was unable to find any difference between the two groups. By contrast, Buscaino (1958) claims to have found qualitative differences in urinary indoles in schizophrenia.

#### SUMMARY

1. Urinary indole excretion was studied by two-dimensional paper chromatography in 63 normal subjects, 65 schizophrenics, 60 cases of miscellaneous mental illness, 31 new admissions to a psychiatric observation ward and 35 cases of physical illness from a general hospital.

2. The three groups of mentally-ill subjects showed a higher total of indole spots on their urine chromatograms than did the other two groups. The increases were most marked in two unknown indoles, and they occurred most frequently in acutely ill patients.

3. No evidence was obtained for an abnormal indole excretion greater than about 10 mg./24 hours in mentally ill subjects.

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# THE EFFECT OF AUDITORY STIMULUS INTENSITY ON THE REACTION TIME OF SCHIZOPHRENICS

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## INTRODUCTION

Two earlier studies (Venables and Tizard, 1956a, b) on the reaction time (RT) of schizophrenics have shown that as the intensity of a visual stimulus is increased beyond an optimum point, RT to the stimulus increases. This "paradoxical" increase in RT is not shown by normal subjects, whose RT decreases as the intensity of visual stimulus increases. It was also found that the paradoxical phenomenon with visual stimuli was only shown on an initial occasion of testing. When the experiment was repeated twenty-four hours later, although there was no alteration in the mean level of RT, the pattern of increase in RT with increasing intensity, previously found, was absent.

Studies by Pieron (1919) and Chocholle (1954) have shown that with normal subjects the RTs to auditory stimuli also decrease as the intensity of the stimulus increases. The present experiments were carried out to determine whether with schizophrenics the effect on RT of a strong auditory stimulus would be similar to the paradoxical effect of a strong visual stimulus. A preliminary experiment with five female schizophrenics and an auditory stimulus of 1,000 c.p.s. at intensities of 30, 45, 60, 70 and 90 db. presented through earphones indicated that no paradoxical effect was present, and the relationship was one of decreasing RT to increasing auditory stimulus intensity.

This finding, which was contrary to that which had been obtained with visual stimuli with schizophrenics, made further experimentation necessary.

## METHOD

To establish that the experimental conditions and type of subject were similar to those with which paradoxical effects had been observed in the previous studies using visual stimulation, subjects were tested with visual as well as auditory stimuli. Subjects were allocated at random to one of two groups, one of which made 20 consecutive responses to each of five intensities of visual stimuli, and then to each of five intensities of auditory stimuli, while the other group responded first to the five auditory intensities and then to the five visual intensities. In each set of five intensities responses to the first served as a practice run, and the intensity of stimulus for this practice run was the same for all subjects. The remaining four stimuli were presented in balanced Latin Square order to obviate order effects. The use of a practice run was thought to be necessary because the preliminary experiment had suggested that the responses

to the first auditory stimulus might be markedly longer than those to the remaining stimuli among which no order effect was apparent.

The subject reacted to the appearance of the stimulus by switching it off with a small toggle switch, after which he returned the switch to its previous position to await the next stimulus. A switch rather than a key was used as its action was more easily understood by severely ill schizophrenics. Auditory stimuli of frequency 1,000 c.p.s. were presented by means of earphones fed from a pure tone audio-generator. The practice stimulus in each case was of 60 db., and the test series were of intensities 30, 50, 70 and 90 db. These intensity values are referred to a level of 0.0002 dynes/cm<sup>2</sup> at 1,000 c.p.s. The visual stimulus consisted of a ground glass screen 0.75 inches in diameter, illuminated from the rear. Change in intensity was made by the insertion of neutral density filters behind the screen. The practice stimulus was 60 foot candles, and the test series used intensities of 16, 135, 600 and 1,500 foot candles. A forewarning bell, which could be heard with the earphones in place, preceded by three seconds the onset of the stimulus which was turned off by the subject's reaction. If the subject failed to respond, the stimulus remained on for three seconds. The cycle of warning and stimulus was repeated once every eight seconds. Twenty responses were given to each intensity of stimulus and a three-minute rest period was allowed between each series of twenty responses. Measurement of the time of each response was made to the nearest milli-second. Sixteen male and sixteen female schizophrenics were tested. The mean age of the male patients was 38.3 S.D. 7.28 years and of females 43.6 S.D. 9.8 years; all patients in this and the other experiments reported here were under fifty-five years of age. All were non-paranoid chronic schizophrenics who had been in hospital longer than two years. None had had leucotomy or were receiving physical treatment at or near the time of the experiment.

## RESULTS

In order to avoid the possible effects of warm up and end spurts, only responses 6-15 of the total twenty responses to each intensity of stimulus were used for analysis.

TABLE I  
*Mean Values of Reaction Time (in seconds) Obtained with Various Intensities of Visual and Auditory Stimulation*

|                 |    |    |    | Stimulus Intensities (foot candles and decibels) |      |     |       |    |
|-----------------|----|----|----|--------------------------------------------------|------|-----|-------|----|
| Experiment 1    |    |    |    | Visual Stimuli                                   |      |     |       |    |
|                 |    |    |    | 16                                               | 135  | 600 | 1,500 | N  |
| Group A*        | .. | .. | .. | .74                                              | .67  | .69 | .74   | 16 |
| Group B         | .. | .. | .. | .77                                              | .71  | .69 | .68   | 16 |
| Experiment 1    |    |    |    | Auditory Stimuli (1,000 c.p.s.)                  |      |     |       |    |
|                 |    |    |    | 30                                               | 50   | 70  | 90    |    |
| Group A*        | .. | .. | .. | .97                                              | .90  | .78 | .71   | 16 |
| Group B         | .. | .. | .. | 1.17                                             | 1.05 | .97 | .75   | 16 |
| Experiment 2    |    |    |    | Auditory Stimuli (white noise)                   |      |     |       |    |
|                 |    |    |    | 60                                               | 75   | 95  | 115   |    |
| Single occasion | .. | .. | .. | .95                                              | .88  | .80 | .77   | 8  |
| Experiment 3    |    |    |    | Auditory Stimuli (200 c.p.s.)                    |      |     |       |    |
|                 |    |    |    | 50                                               | 70   | 90  | 98    |    |
| Single occasion | .. | .. | .. | .73                                              | .67  | .57 | .53   | 8  |

\* Where Group A is group tested first on visual stimuli and then on auditory stimuli, and Group B is group tested first on auditory stimuli and then on visual stimuli.



The upper part of Table I shows the mean value of RT for each intensity of visual and auditory stimuli. Values are given separately for groups of responses given first or second in the testing session.

It is seen from Table I that with visual stimulation given first, after an initial drop in RT from stimuli of 16 foot candles to 135 foot candles, there is thereafter a rise in RT as stimulus intensity increases. This pattern is shown by thirteen out of sixteen subjects, a proportion significant at the .05 level by the Sign test.

This pattern is not shown when visual stimuli appear second, a rise in RT being shown by only four out of sixteen subjects.

These results are similar to those previously obtained and indicate the phasic nature of this paradoxical phenomenon by its disappearance on a second occasion of testing.

It is thus established that the conditions and type of subject are such that significant paradoxical effects may be obtained in the visual modality; and the results obtained with auditory stimulation can now be examined.

Mean values of RT for the four intensities of auditory stimulation show no evidence of a rise in RT with increasing intensity and examination of individual figures shows that only three out of sixteen subjects show a rise in RT on the first occasion of testing, and four out of sixteen on the second.

Lack of evidence of a paradoxical effect with stimuli of 1,000 c.p.s. might possibly be due to stimulation using only a single pure frequency. A parallel with white light is provided by white noise. A second experiment was therefore carried out with sound of this nature to see if the presumed activation of a larger number of nerve endings would result in appearance of paradoxical effects.

White noise was presented by means of an amplifier and loudspeaker having a wide frequency response to give optimum reproduction of a full range of frequencies. In addition, intensities greater than had been possible with earphones were used to explore the effect of very intense stimuli. The test series used values of 60, 75, 90 and 115 db. Eight male, chronic, non-paranoid unleucotomized schizophrenics, who were not under treatment and who had not been previously tested, were tested; their mean age was  $48.8$  S.D.  $8.4$  years.

Examination of the central part of Table I (Experiment 2), shows that no evidence of lengthening of response latency, even with the high intensities employed, was given. Only two of the eight subjects showed a rise in RT with increasing auditory stimulation.

Before considering the evidence for lack of paradoxical effect as final, it was decided to perform a third experiment using a stimulus of 200 c.p.s., and with no forewarning signal. The frequency of 200 c.p.s. was adopted as being well below that of 800 c.p.s. where, as shown in an experiment by Stevens and Davis (1938, p. 395), a sudden drop in the action potential in the auditory nerve occurs. "Above this critical frequency the individual fibres cannot follow the frequency of the stimulus, but must respond to every other vibration." At 200 c.p.s., even allowing for anomalies due to possible deficits in neurone transmission and abnormal length of refractory phase in schizophrenics, it is likely that maximum potential in the auditory nerve for a particular intensity will be achieved.

The forewarning signal was omitted in this experiment because it was thought possible that the alerting of the auditory system by a warning in the same modality as the stimulus might be responsible for the non-appearance of the paradoxical effect.

Intensities of 50, 70, 90 and 98 db. were used for test trials. The practice trial employed an intensity of 80 db. The stimulus tone was presented through a loudspeaker in the same manner as the white noise. The subjects were eight male chronic non-paranoid unleucotomized schizophrenics who were not under treatment at the time of the experiment, and who had not previously been tested. Their mean age was 35.65 S.D. 8.75 years.

The bottom part of Table I (Experiment 3) shows the mean values of RT obtained. It is seen that there is no evidence of paradoxical effect and, considering individual results, not one subject showed an increase in RT with increase in stimulus intensity.

With this final negative result it must be considered as established that no paradoxical effect is to be observed in schizophrenics in responses to intense stimuli in the auditory modality.

The degree of consistency of this finding may be most conveniently illustrated by the use of Kendall's (1948) coefficient of concordance,  $W$ . If the results of each subject for each group of four auditory intensities are ranked in order of response speed the concordance of their rankings is shown by a  $W$  coefficient of .355 which is significant by the use of the  $F$  statistic, having a value of 17.1, at well beyond the .001 level for  $d.f.s$  of three and 91.

Lack of effects of the order of the test trials are shown by an  $F$  of 0.258 for the first, 0.398 for the second and 0.220 for the third experiment. None of these values approach significance.

#### DISCUSSION

The findings reported in this paper, although negative, enable the pattern of schizophrenic dysfunction to be clarified somewhat.

One deduction which can be made concerns the site of function of the paradoxical effect, now established in the visual modality with 56 out of the 64 schizophrenics who took part in our two previous studies and the present one. As the final effector pathway is common to RT experiments testing both the visual and auditory modality it is evident that the paradoxical effect may be considered as having its origin at a point in either the receptor organ or in the cortex before the effector pathway. Much further work must be carried out to establish whether this schizophrenic anomaly of function can be considered central or peripheral.

It was established in a previous experiment (1956b) that the extent of the paradoxical phenomenon was related to the initial slowness of the subject's RT. With visual stimuli there was a correlation of  $r=0.74$  between RTs on the weakest stimulus and the slope of a linear regression line representing for each subject the increase in RT from the stimulus of optimum intensity to the brightest stimulus. Examination of the present data for auditory stimuli indicates that the gradient of fall of RT with increasing intensity is also related to initial level of RT and hence probably to severity of illness. A correlation between initial RT and the slope constant (negative) of the linear regression equation summarizing the subjects' performance was found to be .45,  $P<.02$ . It thus appears that the sensitivity of the schizophrenic to changes in stimulus intensity is related to his slowness of response and hence, in so far as the latter is related to severity of illness (King, 1954), to his pathological condition. This is contrary to what one would expect, in that the withdrawn, severely ill schizophrenic appears to be the patient who is least responsive to his environment. It may however be that it is his pathological sensitivity to changes in his environment which causes him to withdraw to a state where changes are least felt.

A third anomaly which needs further research to put it on more than a suggestive footing, is the finding that in the first experiment (cf. Table I) responses to all but the loudest intensity of auditory stimulation are longer than those to visual stimulation. This is a reversal of the usual finding with normal subjects. Teichner (1954) makes the statement that "there is no evidence available that indicates whether or not the RT varies according to the receptor system stimulated", but he goes on to say that in fourteen studies it is reported that auditory RT was found to be faster than visual RT. The data in Table I are thus suggestive of a yet further anomaly in the performance of schizophrenics.

#### SUMMARY

Experiments carried out have shown no evidence for the appearance in schizophrenics of paradoxical increase in reaction time with increase in auditory stimulus intensity. This phenomenon has previously been established for schizophrenics with visual stimulation, and the present experiments gave, with visual stimuli, further evidence of its existence. Implications of the difference of results between the two sensory modalities are discussed.

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# PHENYTOIN TOXICITY WITH ASSOCIATED MENINGEAL REACTION

By

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PHENYTOIN Sodium (Sodium diphenylhydantoinate) is established in the treatment of epilepsy. Toxic side effects, especially on the nervous system, have been well documented. Untoward reactions may follow therapeutic doses taken over a period of time, or as the result of a single massive dose taken accidentally or with suicidal intent.

The following case of toxic reaction is reported because of the unusual mode of presentation and the associated C.S.F. changes.

## CASE HISTORY

A girl aged 19 years was admitted to hospital on June 1st, 1957, in coma. On examination nuchal rigidity was evident, the limbs were flaccid, all the deep reflexes were brisk and the plantar responses were bilaterally extensor. The gums were grossly hypertrophied so that only the extreme lower margins of the teeth could be visualized. The pulse was regular at a rate of 80/min. No other abnormality was detected in the other systems.

Lumbar puncture was performed. The fluid obtained was clear and colourless at a pressure of 120 mm. of H<sub>2</sub>O and the dynamics were normal. Analysis of the fluid showed

Cells 80 per cent. c.mm. (80 per cent. lymphocytes). Protein 70 mg. per cent.

Glucose 40 mg. per cent. Chlorides 750 mg. per cent.

W.R. negative.

No organisms were detected and the subsequent cultures were negative.

Further information obtained from the relatives indicated that the patient was mentally defective, could neither read nor write and had suffered from epilepsy for the past eighteen months. There had been no previous similar episode.

In January 1957 her general practitioner was advised to prescribe phenobarbitone. After two months of this treatment the attacks had not been influenced and the practitioner changed the treatment to D.P.H. (Epanutin, Parke Davis) 0.1 g. t.d.s.

Nine weeks before her admission she had to stop work because of headaches and dizziness. Her walking was unsteady and she fell frequently. About the middle of May her condition further deteriorated and she was confined to bed because of the increased severity of her ataxia. No further alteration in her condition ensued until three days before admission when the dosage of D.P.H. was raised to 0.4 g. daily. After this she would not eat, drank very little, and occasionally vomited.

Decisions regarding treatment were very difficult, since in the very early stage such possibilities as tuberculosis and other lymphocytic forms of meningitis arose. In view of a normal chest x-ray which was obtained, no antibiotic therapy was adopted.

The patient was tube fed and the D.P.H. was continued at the same dosage with 100 mg. of vitamin C.

Her condition remained unchanged during the next five days. Apart from a slight rise in temperature in the first few hours she was apyrexial throughout. The constipation which had been a feature for a week before admission persisted. The patient was not incontinent of urine in the early stages. Catheterization yielded scanty quantities of urine which unfortunately were not measured, but definitely indicated oliguria. Primidone was substituted for D.P.H. after the fifth day of admission, the change over being completed in three days.

Coinciding with the alteration of anticonvulsant the coma became lighter and restlessness was prominent for 48 hours.

Three days after complete cessation of D.P.H. she was sufficiently conscious to be allowed to sit out of bed and she made steady progress subsequently. Four days later she spoke for the first time and was able to walk very unsteadily to the toilet. Her former level of intellect was regained three weeks after admission but the ataxia persisted for five weeks.

Lumbar punctures were repeated several times and the fluid showed a gradual return to normal. The analysis after five weeks was: Cells 5 per cent. c.mm. Protein 65 mg. per cent.

Specimens of blood were taken on the 14th and 26th June for virus studies. The titres for the second sample were:

*Leptospira icterohaemorrhagica*

Less than 1/10.

" *canicola*

Complement fixation tests for:

Mumps S and V. Adenovirus antigen

Less than  $\frac{1}{4}$ .

Lymphocytic choreomeningitis.

Less than  $\frac{1}{4}$ .

The girl was re-examined in the middle of July. She was in good health, eating very well and able to walk without any unsteadiness. The gingival hypertrophy had resolved.

#### COMMENT

Williamson (1940) from his experience in the treatment of 20 male oligophrenic epileptics came to the conclusion that mentally defective subjects were more prone to the toxic effects of D.P.H. He considered that there was a relationship between intolerance to the drug and pathological changes in the nervous system. The toxic effects, in his series, made an insidious appearance after an average of six weeks treatment.

A search of the literature has revealed only one case comparable to the above. Graveleau *et al.* (1954) (2) described the case of a girl receiving 0.4 g. of D.P.H. daily for seven months after taking 0.3 g. daily for over a year. She presented with diffuse neurological signs including ataxia, nystagmus and sensory changes. The C.S.F. contained 28 cells/c.mm. rising in a few days to 115 cells/c.mm. mainly lymphocytes. The protein rose from 55 mg. per cent. to 70 mg. per cent.

Later C.S.F. findings showed an albumino-cytological dissociation (8 lymphocytes/c.mm. Protein 110 mg. per cent.). Rapid improvement followed withdrawal of the drug. The initial picture was of lymphocytic meningitis with later on albumino-cytological dissociation. They reported the case to draw attention to D.P.H. poisoning mimicking encephalitis.

Slight elevation of the C.S.F. protein has been noted in subjects taking massive single doses but no changes in cytology were reported (3).

It would seem reasonable to incriminate D.P.H. therapy as a basis for the meningeal reaction reported in the present case. There were other significant and well-recognized features of D.P.H. toxicity, for example the gingival hypertrophy, the marked ataxia and increased irritability. The inability to discover any other cause and the favourable response to withdrawal of the D.P.H. further support this conclusion.

#### SUMMARY

An example of meningeal irritation with C.S.F. changes is reported in a mentally defective epileptic girl receiving D.P.H. therapy. Only one comparable case has been discovered in a search of the literature. Recovery followed withdrawal of the drug.

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# SUSCEPTIBILITY TO METHYLPENTYNOL: EYELID CONDITIONING AND P.G.R. RESPONSE

By

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EYSENCK (1957a) has recently cogitated the relation between personality and drug response. He quotes McDougall (1929) as stating "I have observed in a number of cases that the marked extraverted personality is very susceptible to the influence of alcohol. The introvert, on the other hand, is much more resistant to alcohol". This is a remark capable of confirmation, for Eysenck (1953) has described at least two personality dimensions, each a continuum and each orthogonal to the other. These two dimensions were termed "Neuroticism-Normality" and "Extraversion-Introversion". A number of tests have been elaborated by Eysenck (1955, 1956, 1957b) for measuring such personality quantities.

Some of these tests were utilized by Bartholomew and Marley (1958) when scrutinizing a variety of somatic and personality variables that might affect response to methylpentynol ("Oblivon"). They noted that whereas a pronounced correlation existed between high neuroticism scores (as measured on the Maudsley Personality Inventory) and susceptibility to the drug, the only association between extraversion and susceptibility was a just statistically significant relation over the whole of that continuum as determined from the same questionnaire. Methylpentynol is a branched 6-carbon alcohol, and as the activity of an alcohol increases with the size of its molecule (Gaddum, 1956), one might have supposed that the results would have emphasized rather than contradicted McDougall's findings.

The relation between personality dimensions and conditioning ability has been explored by Eysenck (1955) and Franks (1954). Conditionability was discovered to be linked with introversion-extraversion (extraverts condition badly) but was unrelated to neuroticism.

It was decided to investigate the possibility that there might or might not be some association between conditioning (as measured by the eyelid response) and reaction to methylpentynol. In addition, and apart from the possibility

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of substantiating the thesis that susceptibility to the drug is not primarily related to the extraversion-introversion continuum, the opportunity would also present to assess the effect of methylpentynol on conditioning. If it acts as do other central nervous depressants (ethyl alcohol or amylobarbitone sodium) the effect of the drug should be to render the establishment and performance of conditioned responses more difficult. Previously it had been discovered that amylobarbitone sodium depresses, whereas dextroamphetamine sulphate facilitates the formation of conditioned reflexes (Franks and Lavery, 1955; Franks and Trouton, 1958).

### METHODS

The conditioning procedure and apparatus have been described elsewhere (Franks, 1954, 1956) a special sound-proof conditioning laboratory having been constructed for the purpose (Franks, 1955).

The unconditioned stimulus was an air puff, and the conditioned stimulus a tone delivered through a pair of padded earphones. Two responses were recorded: the eyeblink and the psychogalvanic reflex (P.G.R.). A sequence of partial reinforcement was employed so that interspersed among 30 reinforced trials, consisting of an air puff paired with a tone, were 18 test trials (Acquisition trials) during which the tone alone was given. This was followed by 10 successive test trials (Extinction trials) in which, as before, the tone alone was presented. The procedure lasted approximately 25 minutes.

All stimuli were given and controlled electronically, the eyelid movements being measured by a photoelectric cell near the eye of the patient (Franks and Withers, 1955). This novel method of recording eyelid movements is particularly valuable when applied to mentally disturbed, sedated or otherwise abnormal subjects, since, unlike almost all other existing techniques, it is absolved from the cumbersome necessity of having electrodes or artificial eyelashes attached to the testee. On account of the lack of direct contact, many subjects remain unaware of the recording of their eyelid movements. A further refinement is that the small photoelectric cell is mounted on a pair of plain glass spectacles which move in sequence with the testee, who is consequently not constrained to keep his head rigidly still. The stimuli and responses were registered on a continuously recording inkwriting millimeter.

The P.G.R. is a response which purports to assess sympathetic activity by measuring alterations in skin resistance when the subject perspires. It is an unsatisfactory index since the changes recorded depend upon a large number of variables, e.g. room temperature, humidity, atmospheric pressure, as well as the method of application of the electrodes. It was decided, therefore, to record the P.G.R. changes merely as events rather than attempt a quantitative evaluation of their magnitude. The technique employed was the Fere exsomatic method, a current of 14 microamps being passed through the subject (Franks, 1954). The electrodes, which should be dry, are placed on the thenar eminences of both hands.

Twenty-five subjects (9 males, 16 females) aged 19-54 years, in hospital for the treatment of neurotic or psychosomatic disorders, were prescribed 0.5 g. q.d.s. of methylpentynol for 5 days, a base-line of individual reaction being obtained by the immediate prior administration for the same period of an identical number of inert capsules. (The subjects had been weaned from all drugs at least 2-3 days before commencing the inert capsules.) During the 5 day regime of the latter, the Maudsley Personality Inventory was administered and

the initial control conditioning performed. It was imperative that these be done at a time when the individual was not in receipt of drugs, for as previously indicated, conditionability is modified by drugs affecting the central nervous system, and the ingestion of cerebral depressants (amylobarbitone sodium) is associated with an increase of extraversion as measured on the Guildford R scale (Franks and Lavery, 1955). The Maudsley Personality Inventory (adapted partly from the Guildford questionnaires) has been described elsewhere (Eysenck, 1957b; Franks, 1957) and is regarded as being a good measure of introversion-extraversion (a high score indicating extraversion) and of neuroticism. The subjects were finally conditioned on the fourth day of methylpentynol, the test-retest interval ranging from 6-10 days.

The clinical response to methylpentynol was graded into three, the unexpected and considerable incidence of toxic phenomena determining a classification—depending on the presence or absence of abnormal signs in the central nervous system—of nil, minimal, and maximal toxic categories (Marley and Bartholomew, 1958).

The prototypes of these clinical gradings will be briefly portrayed. A maximal toxic reaction (Clinical Grading 3) was deemed to be present if it included a majority of the following picture: dilated pupils reacting sluggishly to all stimuli, sustained nystagmus on conjugate lateral gaze, diplopia, ptosis, loss of tone in the lower facial musculature, dysarthria, and a fine tremor of the protruded tongue. A cerebellar type of ataxia might be found in the limbs or an admixture of this with posterior column type of ataxia and a positive Romberg's sign. Alterations in the mental state included mood disturbance and impairment of attention, concentration and abstract thought. A minimal toxic reaction (Clinical Grading 2) was epitomized by little more than nystagmus on conjugate lateral gaze, and slight unsteadiness of gait or drowsiness. Mood changes were also evident. The designation of nil toxicity (Clinical Grading 1) is self-explanatory.

## RESULTS

### *Conditioning and Personality*

Only the eyeblink response will be considered since there was too much adaptation of the P.G.R. to the unconditioned stimulus for the latter to be regarded as a consistent measure of conditioning. A correlation of  $-0.21$  ( $p > 0.05$ ) was noted between acquisition of the conditioned eyeblink response of the 25 subjects and their rating on the extraversion-introversion scale of the questionnaire. A correlation of  $-0.20$  ( $p > 0.05$ ) was found between resistance to extinction and the rating on the extraversion-introversion scale. The correlations between conditioning and neuroticism were  $-0.048$  ( $p > 0.05$ ) for the acquisition trial and  $-0.059$  ( $p > 0.05$ ) for the extinction trial. (The raw extraversion and neuroticism scores had been corrected so that the two personality dimensions of extraversion-introversion and neuroticism-normality would be independent of one another.) These results, while not statistically significant, are consistent with the argument that conditionability is related to the introversion-extraversion dimension and not to neuroticism.

### *Susceptibility to Methylpentynol, Conditioning and Personality*

The clinical gradings, personality ratings, and the results for the conditioning of the 25 subjects are depicted in Table I.

TABLE I

*Relation Between Clinical Gradings of Susceptibility to Methylpentynol and Mean Extraversion Rating (E), Mean Neuroticism Rating (N), and Mean Number of Conditioned Eyeblink Responses*

| Clinical Grading |    |    |    | E    | N    | Mean Number of Trials for Conditioning Eyeblink Response |            |
|------------------|----|----|----|------|------|----------------------------------------------------------|------------|
|                  |    |    |    |      |      | Acquisition                                              | Extinction |
| 1                | .. | .. | 6  | 9.9  | 9.5  | 7.2                                                      | 2.8        |
| 2                | .. | .. | 9  | 13.0 | 15.2 | 8.3                                                      | 3.8        |
| 3                | .. | .. | 10 | 8.6  | 17.6 | 4.7                                                      | 2.2        |

It is obvious that in this series susceptibility to methylpentynol is unrelated to the extraversion-introversion continuum but appears to be linked with high scores for neuroticism. The relation to conditioning is more obscure, and it might seem from ranking the mean scores for the number of trials required before the establishment of the conditioned eyeblink response that susceptibility to the drug is not associated with conditionability. On the other hand, if the drug dose-response curve is assumed to be steep, which is probable (the curve would be more likely to follow a geometric than an arithmetic progression) the mean acquisition scores of 8.3 and 7.2 for the eyeblink response could be regarded as coming from individuals at the lower end of the dose-response curve, whereas the mean acquisition score of 4.7 would be from subjects at the upper end of the dose-response curve, and the discrepancy in ranking for the minimally susceptible group would be unimportant. A case could therefore be advanced for an association between ease of conditioning and maximum susceptibility to methylpentynol, although no similar trend is apparent between the rate of extinction of the conditioned eyeblink response and susceptibility. It would be more realistic to assume, however, that no real relation has been demonstrated between eyeblink conditioning and liability to intoxication with the drug.

#### *Depressant Effects of Methylpentynol on Conditioning and P.G.R.*

The mean number of conditioned eyeblink responses for each subject prior to and during the regime on methylpentynol are shown in Table II.

TABLE II

*The Mean Numbers of, and Standard Deviations of, Acquisition and Extinction Trials of Conditioned Eyeblink Responses Both Before and With Methylpentynol*

|      |    |    |    | Acquisition Trials    |                     | Extinction Trials     |                     |
|------|----|----|----|-----------------------|---------------------|-----------------------|---------------------|
|      |    |    |    | Before Methylpentynol | With Methylpentynol | Before Methylpentynol | With Methylpentynol |
| Mean | .. | .. | .. | 5.6                   | 6.3                 | 2.1                   | 2.6                 |
| S.D. | .. | .. | .. | 4.1                   | 5.0                 | 1.8                   | 2.2                 |

In order to evaluate the statistical significance of these results, a control group of similar subjects tested and retested after an equal interval without methylpentynol would be required. This information is not available, but data do exist for a group of 20 normal subjects retested after a time lapse of 14-21 days. The mean number of acquisition and extinction conditioned eyeblink responses for this normal control group are presented in Table III.



TABLE III

*The Mean Number of, and Standard Deviations of, Acquisition and Extinction Trials of Conditioned Eyeblink Responses in a Control Group under Test-Retest Conditions*

|      |    |    |    | Acquisition Trials |        | Extinction Trials |        |
|------|----|----|----|--------------------|--------|-------------------|--------|
|      |    |    |    | Test               | Retest | Test              | Retest |
| Mean | .. | .. | .. | 8.0                | 14.4   | 3.7               | 5.6    |
| S.D. | .. | .. | .. | 5.3                | 6.4    | 1.4               | 1.6    |

The group of normal subjects, as expected, increase in eyeblink conditioning significantly from test to retest ( $p < 0.01$ ). The group receiving methylpentynol do not evince an increased conditioning score from test to retest conditioning ( $p > 0.05$ ). Although the two groups are not strictly comparable, the results suggest that methylpentynol reduces conditionability.

Although the P.G.R. data cannot be used as a measure of conditioning since there was often no response to the unconditioned stimulus, they can still be considered as indicators of sympathetic autonomic activity. The mean number of P.G.R. responses to the 18 acquisition test trials for the normal group and for that receiving methylpentynol were compared.

TABLE IV

*The Mean Number of, and Standard Deviations of, P.G.R. Responses in a Group With and Without Methylpentynol, and in a Control Group from Test to Retest*

Methylpentynol Series (25 subjects)

|      |    |    |    |    | Number of P.G.R. Responses Before Methylpentynol | Number of P.G.R. Responses With Methylpentynol |
|------|----|----|----|----|--------------------------------------------------|------------------------------------------------|
| Mean | .. | .. | .. | .. | 3.3                                              | 0.6                                            |
| S.D. | .. | .. | .. | .. | 1.5                                              | 0.6                                            |

Control Series (20 subjects)

|      |    |    |    |    | Number of P.G.R. Responses on Initial Testing | Number of P.G.R. Responses on Retest |
|------|----|----|----|----|-----------------------------------------------|--------------------------------------|
| Mean | .. | .. | .. | .. | 2.5                                           | 3.0                                  |
| S.D. | .. | .. | .. | .. | 1.5                                           | 1.8                                  |

The mean number of P.G.R. responses is significantly reduced after methylpentynol ( $p < 0.05$ ) although no significant alteration in the mean number of P.G.R. responses occurred in the control group from test to retest, suggesting that methylpentynol has a depressant effect on sympathetic conditioning as measured by the psychogalvanic response ( $p > 0.05$ ). Examination of the case records confirms this; thus whereas in the control group, 11 of the 20 subjects gave P.G.R.s initially and 14 gave P.G.R.s on retest, in the group receiving methylpentynol, 14 of the 25 subjects gave P.G.R.s initially but only 3 on retest.

# DISCUSSION

It was hoped in the present investigation to provide evidence that susceptibility to the higher alcohol methylpentynol bore no relation either to extraversion or conditioning. While this has proved correct up to a point, the correlation between extraversion and conditionability was not statistically significant, so that the protocol of this paper would be more suitably confined

to stating that liability to intoxication with methylpentynol and ability to condition seem to be unrelated factors. There was however a definite association between high neuroticism scores on the Maudsley Personality Inventory and susceptibility to the drug.

The results are interesting in that they are at variance with an observation of Pavlov's (Pavlov, 1927). Pavlov noted a difference in the behaviour of his dogs. Certain of the animals developed conditioned salivary responses with ease, which, once established, were retained for a long while. Other dogs developed positive conditioned responses with difficulty, and, once formed, they were easily disrupted and extinguished. Pavlov also noted that animals which conditioned well were resistant to bromides, whereas dogs of the same body weight but which conditioned with difficulty required only an eighth of this amount of bromide and reacted badly to anything in excess.

Methylpentynol possessed a depressant effect on conditioning ability, a finding in conformity with that of Hilgard and Marquis (1940) who noted that central nervous depressants (sodium bromide) retard the formation, and accelerate the rate of extinction of conditioned responses. Methylpentynol may act by blocking the formation of the central changes associated with conditioning, and also by interfering with the peripheral performance of these conditioned responses. A peripheral neuro-muscular blocking activity by this drug has been demonstrated in animals (Quilliam, 1955; Nicholls and Quilliam, 1956).

#### SUMMARY

Twenty-five subjects were prescribed 0.5 g. q.d.s. of methylpentynol for 5 days preceded by a similar period on inert capsules.

During the period on inert capsules, the patient completed the Maudsley Personality Inventory and the control conditioned eyeblink and psychogalvanic responses were obtained. The final conditioned eyeblink and psychogalvanic responses were determined on the fourth day of the course of methylpentynol.

No relation was found between susceptibility to the drug and conditioning ability. Methylpentynol possessed a depressant effect on eyeblink conditioning.

There was no relation between susceptibility to methylpentynol and extraversion scores obtained from the Maudsley Personality Inventory, although there seemed a definite association between high neuroticism scores determined from the same questionnaire and susceptibility to the drug.

Methylpentynol has a depressant effect on sympathetic conditioning as measured by the psychogalvanic response.

#### ACKNOWLEDGMENTS

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# DISTANCE CONSTANCY IN SCHIZOPHRENIC PATIENTS\*

By

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RECENT research has shown that constancy of perception breaks down in schizophrenics. Size constancy in these patients has been investigated by Raush (13, 14), Weckowicz (16), and Crookes (2). Raush found that paranoid schizophrenics had increased size constancy compared with normals and other schizophrenics. He predicted that in other types of schizophrenia size constancy might be poorer than in normals. However the difference he found was not statistically significant. Weckowicz found that chronic hospitalized schizophrenics had poorer size constancy than other hospitalized patients and normals. These two investigators determined size constancy by instructing the subjects to adjust the size of an object (a rod or a square) to the size of a standard object at a distance. Crookes used a direct method. His subjects were instructed to reproduce the size of the image of the standard object seen at a distance and not the size of the object itself. He came to the same conclusion as Weckowicz that size constancy in schizophrenic patients was impaired.

The literature on size constancy has been summarized elsewhere (16). It is sufficient here to say that size constancy denotes the ability to perceive the size of an object stable within wide limits in spite of the change of the size of the retinal image with the distance from which the object is seen. The relationship between perceived size and distance in visual space has been studied in normal people by Boring and Holway (9), Brunswik (1), Gibson (5, 6), Ittelson (10), and Gilinsky (7, 8). These authors have found that size constancy is closely related to distance constancy. It depends on an ability to take into account the distance of the perceived object. A retinal image of the same size can be produced either by a small object at a near distance or a large object at a far distance, so there is a reciprocity between the perceived distance and perceived size. They are two aspects of the same phenomenon. Moreover, the ability to perceive the size of an object as constant at different distances depends on the ability to perceive in the terms of the three-dimensional

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Euclidian space, where the units of distance remain constant and where there is no foreshortening of space with increased distance.

A standard physical unit of distance, for instance one yard, subtends progressively smaller visual angles with the increased viewing distance (see Fig. 1).

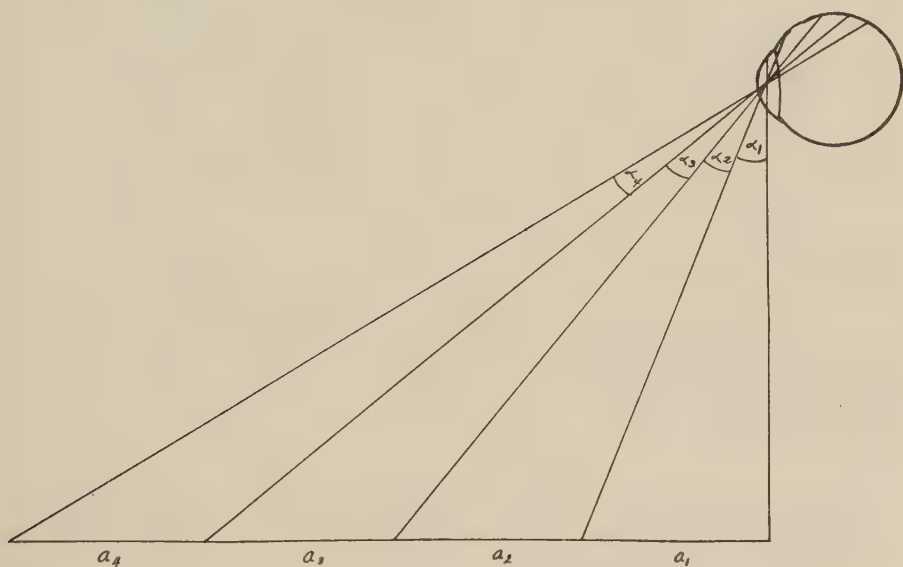


FIG. 1.—Perception in accordance with distance constancy.

Distance intervals:  $a_1 = a_2 = a_3 = a_4$ .

Visual angles:  $\alpha_1 > \alpha_2 > \alpha_3 > \alpha_4$ .

In accordance with distance constancy, the progressively shrinking retinal image corresponding to the progressively diminishing visual angles is “interpreted” as being subtended by a constant unit of distance. The distance gradient of the progressively diminishing visual angles subtending a unit of space is interpreted by using the other gradients of the visual field such as the gradient of the diminishing retinal image of a receding object or the various gradients of texture patterns (5).

In perception where distance constancy is absent, a “subjective unit” of distance is that distance interval which subtends the same visual angle irrespective of the distance from which it is viewed. The same visual angle is subtended by progressively longer units of distance with the increase of the viewing distance (see Fig. 2).

From Figure 2, it can be seen that in perception in accordance with the visual angle constancy (retinal image is the same size) there is a gradient of rapidly increasing units of distance which are perceived as being equal.

In normals, perception as determined by experimental procedures is neither completely governed by distance constancy nor by visual angle constancy, but lies between them, although it probably accords more closely with the principles of distance constancy.

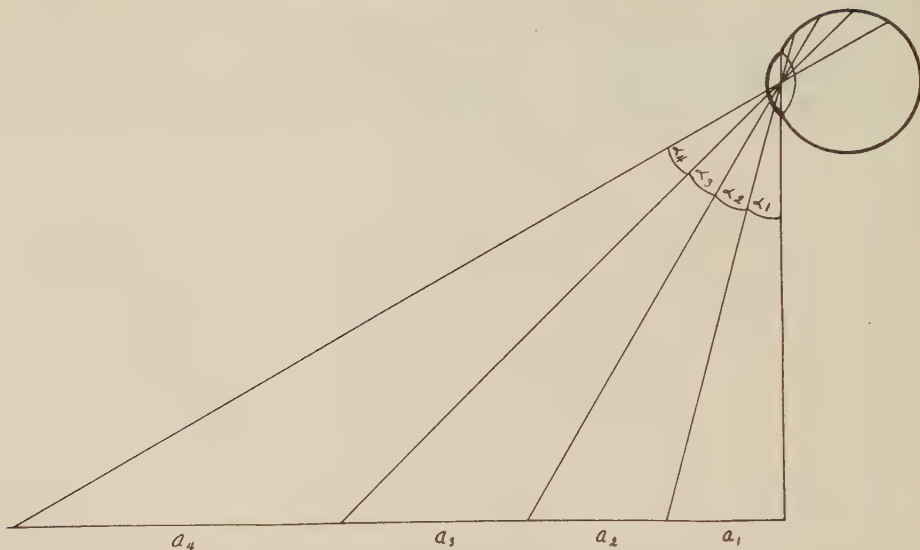


FIG. 2.—Perception in accordance with “visual angle constancy” (distance constancy non-existent).

Visual angles:  $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4$ .

Distance intervals:  $a_1 < a_2 < a_3 < a_4$ .

#### HYPOTHESIS

As there is a relation between size constancy and distance constancy and as schizophrenics have been found to have poorer size constancy than non-schizophrenics, it can be expected:

1. That they have poorer distance constancy than non-schizophrenics.
2. That those schizophrenic patients who have poor size constancy should also have poor distance constancy.

This paper is a report of an experiment, whose purpose was to test these hypotheses.

#### SAMPLE

Two groups were used: 20 schizophrenic patients and 17 normal controls. The schizophrenic sample included only patients in whom the diagnosis of schizophrenia had been firmly established by all psychiatrists who had examined them. It consisted of 5 females and 15 males. Seven patients were diagnosed as hebephrenic schizophrenics, three as paranoid schizophrenics, two as catatonic schizophrenics, one as a simple schizophrenic, and six as undifferentiated schizophrenics.

The mean age was 38 years (S.D.=7.32). The average length of stay in the hospital was 9 years (S.D.=5.07). No patient in whose case there was a possibility of mental deficiency or organic brain disease was included. No patient undergoing insulin or electrical shock treatment was included. Only patients who were co-operative during the experiment were included in the sample. All the patients had their eyes tested and had corrected visual acuity 20/20.

The normal sample included 17 volunteers from the hospital staff, 11 males, and 6 females. The mean age was 28 years (S.D.=7.72).



## EXPERIMENTAL PROCEDURE

An outdoor experiment was carried out on a flat open prairie with an open horizon. A small cart with a white triangular marker was moved by a series of strings and pulleys away or towards the subject. It was held on a straight path by a white nylon rope stretched from an iron peg at the subjects' feet to another peg 220 yards away. Another marker with a white triangle of the same size and shape as the triangle on the cart was used for marking standard distances. For marking one-yard intervals, a red-painted peg was used. The strings and pulleys were operated by an assistant who stood behind the subject.

The experiment consisted of four parts: In the first part both the movable marker (on the cart) and the other marker were placed at 60 yards distance from the subject. The following instruction was read to the subject: "These two triangles are the same distance from you. The right-hand side triangle can be moved either away from you or towards you. We are going to move the right-hand side triangle away from you. Would you tell us to stop when the right-hand side triangle is the same distance from the left-hand side triangle as the left-hand side triangle is from you. In other words, would you tell us to stop when the left-hand side triangle is half-way between you and the right-hand side triangle." The distances were measured in yards.

In the second part both markers were placed at 120 yards distance from the subject and the following instruction was read: "These two triangles are the same distance from you. We are going to move the right-hand side triangle towards you. Would you tell us to stop when the right-hand side triangle is half-way between the left-hand side triangle and you." The distance estimated by the subject was measured in yards.

In the third part the markers were placed at the 60 yards distance and the instruction was the same as in the second part.

In the fourth part only the movable marker was used. The cart was placed right at the feet of the subject. The following instruction was read: "We are going to move this cart away from you, would you tell us to stop when the near side of the cart is one yard from you." After the subject said "Stop", he was told to turn his back. The distance estimated by the subject as one yard was measured and a red peg was driven into the ground to mark it. The subject was told to face ahead again and the following instruction was read to him: "We are going to move this cart away from you again. Would you tell us to stop when the near side of the cart is one yard from the red peg." The subject was again told to turn his back. The distance from the red peg to the near end of the cart was measured. The red peg was removed from its previous spot and driven into the ground just in front of the near side of the cart. This procedure was repeated 20 times.

Thus in the first part of the experiment the subject was instructed to double the standard distance and in the second and third parts to divide the standard distance into halves. In the fourth experiment he was instructed to estimate successive one-yard intervals, judging the first yard from the point where he was standing and subsequent yards from the point where the preceding interval had been judged.

With perfect distance constancy the subjects should double exactly the first standard distance, divide into halves the next two standard distances and estimate as one yard 20 equal distance intervals.

Over-estimation of the distant halves in the first three parts of the experiment and progressive over-estimation of one-yard interval indicates a breakdown of distance constancy.

## RESULTS

The distribution of the schizophrenic sample was badly skewed, due to extreme over-estimation of the far distances by two subjects, so non-parametric statistical methods\* were used in analysing the data. The difference between the estimations of the farther halves of the distances given by the normals and schizophrenics in the first three parts of the experiment is in the expected direction, but not statistically significant. For each task the mean rank was calculated for the normals and the schizophrenics and the significance of these ranks was tested by the Mann-Whitney *U* Test. The results are reproduced in Table I.

TABLE I  
*Mean Rank of Estimations*

|                |    | Part 1            | Part 2             | Part 3            |
|----------------|----|-------------------|--------------------|-------------------|
|                |    | Doubling          | Halving            | Halving           |
|                |    | 60 Yards Distance | 120 Yards Distance | 60 Yards Distance |
| Schizophrenics | .. | 17.65             | 17.64              | 18.59             |
| Normals        | .. | 20.59             | 20.15              | 19.35             |
| Z              | .. | 0.82              | 0.70               | 0.21              |
|                |    | 0.3 > p > 0.2     | 0.3 > p > 0.2      | 0.5 > p > 0.4     |

In both normals and schizophrenics, the objective lengths of the subjective yards increased with the distance away from the subject. These increasing lengths formed a certain gradient. The gradient was much steeper in the schizophrenics, than in the normals. The results of the Median Test are presented

TABLE II  
*Estimates of Successive One-Yard Intervals*

| Successive Yard Judgments |    |    | Median Estimate (Inches) |         | $\chi^2$ | <i>p</i>      |
|---------------------------|----|----|--------------------------|---------|----------|---------------|
|                           |    |    | Schizophrenics           | Normals |          |               |
| 1                         | .. | .. | 41.5                     | 38      | 0.43     | N.S.          |
| 2                         | .. | .. | 44.5                     | 39      | 1.74     | N.S.          |
| 3                         | .. | .. | 45                       | 45      | 0.00     | N.S.          |
| 4                         | .. | .. | 50.5                     | 48      | 1.74     | N.S.          |
| 5                         | .. | .. | 58.5                     | 51      | 1.74     | N.S.          |
| 6                         | .. | .. | 60.5                     | 61      | 0.43     | N.S.          |
| 7                         | .. | .. | 67                       | 65      | 0.43     | N.S.          |
| 8                         | .. | .. | 83                       | 65      | 6.97     | p < .01       |
| 9                         | .. | .. | 84.5                     | 66      | 1.74     | N.S.          |
| 10                        | .. | .. | 104                      | 68      | 3.92     | .05 > p > .01 |
| 11                        | .. | .. | 113                      | 69      | 6.97     | p < .01       |
| 12                        | .. | .. | 116                      | 76      | 10.90    | p < .001      |
| 13                        | .. | .. | 129                      | 76      | 6.97     | p < .01       |
| 14                        | .. | .. | 145                      | 75      | 6.97     | p < .01       |
| 15                        | .. | .. | 141                      | 73      | 6.97     | p < .01       |
| 16                        | .. | .. | 160.5                    | 77      | 15.70    | p < .001      |
| 17                        | .. | .. | 142                      | 82      | 10.90    | p < .001      |
| 18                        | .. | .. | 170                      | 86      | 15.70    | p < .001      |
| 19                        | .. | .. | 177                      | 89      | 10.90    | p < .001      |
| 20                        | .. | .. | 176                      | 89      | 10.90    | p < .001      |

in Table II. The Chi-squares for the first eight one-yard estimations are non-significant while the following 12 Chi-squares are significant and become progressively larger.

\* Distribution free statistics, which are more conservative and do not allow extreme single scores to bias the results.

The successive subjective yards were estimated by different subjects at different distances because the subjects who over-estimated the first few yards estimated subsequent yards from a greater distance than subjects who made shorter estimations of the first few yards. To avoid this confounding of individual yard estimations with the distances from which these estimations were made, the yard estimations by the normals and the schizophrenics made at the same distances were compared. (If there was no yard estimations at a particular distance the nearest one above or below was used.) Twenty-eight estimations of one-yard intervals were used. The differences between the estimations of both groups were tested by the Median Test. The results are summarized in Table III.

TABLE III

| The Distance<br>at Which the<br>Estimation<br>was Made<br>(yards) |    |    | Median Estimate |         | $\chi^2$ | <i>p</i>             |
|-------------------------------------------------------------------|----|----|-----------------|---------|----------|----------------------|
|                                                                   |    |    | Schizophrenics  | Normals |          |                      |
| 0                                                                 | .. | .. | 39              | 38      | 1.00     | N.S.                 |
| 1                                                                 | .. | .. | 50              | 39      | 2.79     | N.S.                 |
| 2                                                                 | .. | .. | 45              | 44      | 0.47     | N.S.                 |
| 3                                                                 | .. | .. | 51              | 46      | 0.47     | N.S.                 |
| 4                                                                 | .. | .. | 51.5            | 50      | 0.11     | N.S.                 |
| 5                                                                 | .. | .. | 54.5            | 50      | 0.47     | N.S.                 |
| 6                                                                 | .. | .. | 62.5            | 61      | 0.10     | N.S.                 |
| 7                                                                 | .. | .. | 60.5            | 62      | 0.47     | N.S.                 |
| 8                                                                 | .. | .. | 70              | 62      | 1.80     | N.S.                 |
| 9                                                                 | .. | .. | 73.5            | 62      | 2.79     | N.S.                 |
| 10                                                                | .. | .. | 79              | 63      | 2.79     | N.S.                 |
| 11                                                                | .. | .. | 84.5            | 64      | 4.05     | .05 > <i>p</i> > .01 |
| 12                                                                | .. | .. | 85              | 67      | 7.20     | <i>p</i> < .01       |
| 13                                                                | .. | .. | 95.5            | 68      | 2.79     | N.S.                 |
| 14                                                                | .. | .. | 104             | 66      | 7.20     | <i>p</i> < .01       |
| 15                                                                | .. | .. | 104             | 71      | 9.03     | <i>p</i> < .01       |
| 16                                                                | .. | .. | 108.5           | 82      | 9.03     | <i>p</i> < .01       |
| 17                                                                | .. | .. | 111             | 76      | 4.05     | .05 > <i>p</i> > .01 |
| 18                                                                | .. | .. | 115             | 76      | 5.46     | .05 > <i>p</i> > .01 |
| 19                                                                | .. | .. | 104.5           | 76      | 5.46     | .05 > <i>p</i> > .01 |
| 20                                                                | .. | .. | 115             | 78      | 9.03     | <i>p</i> < .01       |
| 21                                                                | .. | .. | 118             | 77      | 9.03     | <i>p</i> < .01       |
| 22                                                                | .. | .. | 127.5           | 77      | 5.46     | .05 > <i>p</i> > .01 |
| 23                                                                | .. | .. | 129.5           | 83      | 9.03     | <i>p</i> < .01       |
| 24                                                                | .. | .. | 135.5           | 80      | 11.25    | <i>p</i> < .001      |
| 25                                                                | .. | .. | 141.5           | 78.5    | 7.20     | <i>p</i> < .01       |
| 26                                                                | .. | .. | 141.5           | 82      | 7.20     | <i>p</i> < .01       |
| 27                                                                | .. | .. | 152             | 82      | 11.25    | <i>p</i> < .001      |
| 28                                                                | .. | .. | 152             | 84      | 11.25    | <i>p</i> < .001      |

It can be seen from Table III, that estimations of one-yard lengths at the same distances made by the schizophrenics are greater than those made by the normals. At long distances these differences become very significant.

The schizophrenic subjects had size constancy estimated by the method described elsewhere (16). The two experiments were carried out within 4 weeks of one another. As was reported in the previous paper, size constancy measurements have a relatively high reliability on retest (16).

In order to find the relation between size constancy and distance constancy the estimations of the distances were related to the estimations of sizes. In the size constancy experiment the subjects reproduced by adjusting a rod in front



of them the size of another rod at 7.5 m. distance and at 15 m. distance. It was assumed that those subjects who under-estimated the distance would under-estimate the size and vice versa. In the distance constancy experiment an under-estimation of a distance would mean a longer distance, corresponding to a certain number of estimated yard intervals and an over-estimation of a shorter distance corresponding to the same number of yard intervals. Therefore the subjects were ranked according to the objective length of the distances that they had estimated as eight yards and also according to that which they estimated as sixteen yards. (The cumulative objective lengths of the first eight and the first sixteen-yard intervals were used as the measures.) The distances of eight and sixteen yards corresponded approximately to the distances of 7.5 m. and 15 m., used in the size constancy experiment.

The ranking was from the shortest distance to the longest distance. The same subjects were next ranked on their size estimation of the standard object at the 7.5 m. distance and the 15 m. distance. The ranking was from the greatest estimation to the smallest estimation.

The Spearman Rank Difference correlation coefficient was found between the lengths of the first eight-yard interval estimations and the estimations of the size of the standard object at 7.5 m. The same procedure was repeated for the lengths of the first sixteen-yard interval estimations and the estimations of the size of the standard object at 15 m.

For the 8-yard distance estimation and size estimation at 7.5 m.:

$$\rho = +0.47 \quad .05 > p > .01$$

For the 16-yard distance estimation and size estimation at 15 m.:

$$\rho = +0.39 \quad .05 > p > .01$$

Thus correlations are in the direction predicted by the theory and are significant in spite of the time interval between the two experiments and the very different settings.

## DISCUSSION

The results of this experiment indicate that distance constancy is poorer in schizophrenics than in non-schizophrenics and also that it is related to the poorer size constancy found in these patients. There exists the possibility that the difference between the two groups was due to the fact that the schizophrenics had been hospitalized for many years, that they had been "shut in" in a building and that their poor performance was due to their lack of practice in making judgments of distance. However, almost all the schizophrenic patients used as subjects were parole patients, who spent most of the time out-of-doors in the summer, and were probably more familiar than most of the staff with the fields adjacent to the hospital.

The size constancy and distance constancy studies indicate that the visual perception in schizophrenic patients lacks depth compared with the visual perception of non-schizophrenics. The extent of foreshortening is greater. The perceived gradient of equi-distance intervals in depth of the visual field is much steeper and reaches zero value sooner in schizophrenics than in normals. Therefore, these patients live in a "flatter" world than normals do. They do not integrate the third dimension into the visual field to the same extent as the normals do. As the result of this lack of depth of perception, schizophrenics perceive more in the terms of two-dimensional perspective geometry than do normals, who perceive more in the terms of the three-dimensional Euclidian geometry. Gibson (5), has introduced two important concepts, "visual field"

and "visual world". The "visual field" type of perception is a perception in accordance with the retinal image and perspective geometry, where two parallels meet and where third dimensions are indicated only by diminishing gradients of the sizes of objects and distance intervals. The seen world is like a photograph completely in two dimensions and in the perpendicular plane to the line of vision. The "visual world" type of perception is perception in accordance with size and distance constancy and Euclidian geometry, where two parallels do not meet and perception is wholly three-dimensional. Neither schizophrenics nor normals perceive completely in the terms of "visual field" or in terms of "visual world", the actually perceived world is a compromise between the two. In both groups perception at near distance is much closer to Gibson's visual world and at far distance is much closer to his "visual field". In both groups a point is reached where perception is completely in terms of "visual field", for instance, the perception of the dome of the sky with the sun, the moon and the stars\*. However, both the studies of size constancy and distance constancy indicate that visual perception in schizophrenics is shifted more in the direction of the "visual field" and that of normals in the direction of the "visual world". In schizophrenics the third dimension is less integrated into the perceived world and the limit of the three-dimensional perception is reached sooner than in normals. To put it in other words, the transition from the three-dimensional space to the two-dimensional plane is more rapid.

Gilinsky (7), using diminishing gradients of equal space intervals in the perceived world, has developed the concept of limited, subjective space, ending at a distance where perception becomes wholly two-dimensional and further perception of depth is impossible (the sky with the astronomical bodies). This subjective space is different in different subjects and in different conditions. It appears that on average this subjective limited space is smaller, more constricted in schizophrenics than in normals†.

The lack of depth and "flatness" of the visual world of schizophrenics has theoretical implications for the phenomenology of schizophrenia. Together with impaired form constancy it can change, foreshorten, and distort the appearance of the perceived objects. Perhaps this change in depth perception would account for the complaint of some schizophrenics that things look different, unfamiliar and strange, that they are unreal, grotesque, menacing, as if they were painted or cut out of cardboard.

There are also other intriguing possibilities. Visual perception in the terms of plane geometry is more literal—the size of the retinal image is interpreted literally, while in perception in the terms of Euclidian three-dimensional geometry the perceived size of the object is related to its distance, therefore this type of perception is more relativistic. The lack of three-dimensionality in perception may influence thinking in schizophrenics in the direction of literalness and concreteness and also it may influence their perceived body and their self-concept in the direction of ego-centricity and a poor differentiation of self from non-self. There is some evidence that in these patients perception of time is also changed (11). Thus, there is a possibility that in schizophrenia both the space and time perspectives are changed and distorted, which would account for the strangeness of the world they are living in. This has been studied clinically by phenomenologists (3, 4, 12, 15), but is now being studied experimentally.

\* Some people can assume a sophisticated perceptual set, where they perceive in the terms of Gibsonian "visual field"; this is very important for realistic artists as can be seen for instance in early French impressionists.

† In another paper this concept of subjective space as applied to schizophrenic patients will be developed more formally.

## SUMMARY

1. Distance constancy was studied in schizophrenics and normals.
2. Distance constancy is poorer in schizophrenics than in normals.
3. This is related to their poorer size constancy.
4. The result of poor distance constancy is that visual perception in schizophrenics is lacking in depth and that these patients live in a "flatter" world.
5. The implications of this finding are discussed.

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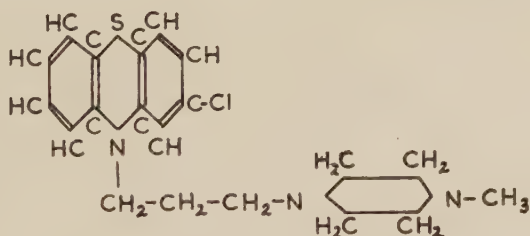
# A CLINICAL TRIAL COMPARING PROCHLORPERAZINE ("STEMETIL") WITH CHLORPROMAZINE ("LARGACTIL") IN THE TREATMENT OF CHRONIC PSYCHOTIC PATIENTS

By

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CHLORPROMAZINE ("Largactil") was introduced to this country some five years ago, and since that time a considerable number of reports on its clinical efficacy have appeared, including Anton-Stephens (1954) and Garmany *et al.* (1954). There is now general agreement that it is a useful form of treatment in chronic schizophrenia, especially for the aggressive, disturbed patient (Salisbury and Hare, 1957). More recently another phenothiazine derivative, incorporating a piperazine ring in the side chain, has been produced. This substance is Prochlorperazine ("Stemetil"), the full title of which is 2-chloro-10-(3-4'-methyl-1'-piperazinopropyl)-phenothiazine, the structural formula being:



It is prepared for use in the form of its dimaleate salt, which contains 62 per cent. of the active base. This compound has shown useful clinical activity in the treatment of Ménière's syndrome and migraine and as an anti-emetic, the last mainly in France. Pharmacologically, prochlorperazine has been shown to have an anti-emetic action, as measured against the action of apomorphine, approximately four times as powerful as that of chlorpromazine. On the other hand prochlorperazine has been found to be two or four times less powerful than chlorpromazine in its potentiating effect on general anaesthetics, hypnotics and analgesics, such as ether, hexobarbitone, and morphine. Prochlorperazine has been used in psychiatry in the United States (Vischer, 1957), and France (Borel *et al.*, 1957; Brousselle *et al.*, 1957; Lecompte *et al.*, 1957), but no reports on its psychiatric applications had, at the time of writing, yet been published in this country\*. As the use of chlorpromazine is so widespread in psychiatric practice, and few, if any, psychiatrists have not by now reached

\* An article on "A Clinical Trial of Stemetil" by H. B. Milne and F. Berliner appeared in the *Journal* for July 1958.

a conclusion as to its efficacy, it was felt that the most practical assessment of the value of prochlorperazine in psychiatry would be a clinical comparison of the two drugs. The trial now described is an attempt to compare the efficacy of prochlorperazine ("Stemetil") with that of chlorpromazine ("Largactil"), in the treatment of aggressive, disturbed, chronic psychotic male patients. In addition, a comparison of the incidence of side effects of the two drugs is made.

Fifty aggressive, disturbed, chronic male psychotic patients (forty-six schizophrenic, two G.P.I., and two M.D.) were selected for the trial on the grounds that they were the most aggressive and disturbed male patients in the hospital who were not at that time undergoing or had not recently undergone some other form of treatment. Two had previously been leucotomized. The patients had all been in hospital for a number of years, the most recent for five years, the longest for fifty-one years, the average being 19.5 years. All were regarded as of poor prognosis. The ages varied from twenty-seven years to seventy-six years with an average of 50.3. An initial assessment of each patient was made in regard to aggression, disturbance, deterioration, and apathy, on a four-point scale (severe, moderate, slight, none), and also for aptitude for social activity and occupation, again on a four-point scale (good, moderate, slight, none). The gradings used were defined as follows:

#### 1. *Aggression*

Severe—frequent physical attacks with minor effects, or occasional physical attacks with serious effects.

Moderate—occasional physical attacks with minor effects, or frequent verbal abuse.

Slight—occasional verbal abuse.

#### 2. *Disturbance*

Severe—frequently extremely noisy and/or frequently requires nursing in side room.

Moderate—occasionally noisy and/or occasionally requires nursing in side room.

Slight—noisy at times but not requiring nursing in side room.

#### 3. *Deterioration*

Severe—needs frequent supervision of toilet and/or appearance.

Moderate—needs regular supervision of appearance.

Slight—needs occasional supervision of appearance.

#### 4. *Apathy*

Severe—no response to efforts to stimulate interest.

Moderate—shows some response to efforts to stimulate interest, but this is required frequently.

Slight—requires only occasional stimulation of interest.

#### 5. *Aptitude for Social Activity*

Good—attends social activities and participates spontaneously.

Moderate—attends social activities spontaneously but does not participate.

Slight—needs encouragement to attend social activities and does not participate.

6. *Aptitude for Occupation*

- Good—pursues occupation without supervision.
- Moderate—pursues occupation but needs occasional supervision.
- Slight—needs constant supervision to remain occupied.

These assessments were made on the basis of the Charge Nurse's estimate taken in conjunction with the author's evaluation. The patients were then divided into two groups, paired as far as possible for aggression, disturbance, deterioration, age, ward, amount of E.C.T. previously given, apathy, aptitude for social activity, and occupation. The first six of these items were regarded as the most important for the purpose of pairing. The amount of E.C.T. previously given was recorded because it had been suggested that there was a positive correlation between the amount of E.C.T. previously given, and the incidence of Parkinsonism and bizarre positions and movements (as described by French and American workers), and it was proposed to test this hypothesis.

The two groups were given one inert tablet t.d.s. for two weeks in order to provide control data establishing the essential similarity of the two groups.

The patients were seen at weekly intervals throughout the trial by the author, and overall progress on a purely clinical basis was noted on a four-point scale (much improvement, moderate improvement, slight improvement, no change) in addition to the noting of progress in the individual items as in the initial assessment.

In the third week one group was given prochlorperazine 12·5 mg. t.d.s. (37·5 mg. daily) whilst the other group was given chlorpromazine 25 mg. t.d.s. (75 mg. daily). The inert tablets and those containing prochlorperazine 12·5 mg. as well as those containing chlorpromazine 25 mg. were all identical, and only the author and the Chief Pharmacist were aware of the design of the experiment. The dosage was increased in each group by one tablet t.d.s. each week, except where there were clinical indications for the dose to be maintained at the previous level, reduced, or for the drug to be withdrawn completely. The maximum dosage in each group was four tablets t.d.s., which in the case of prochlorperazine represented 150 mg. daily, and in the case of chlorpromazine, 300 mg. daily, and was continued for five weeks. Side effects were noted as they occurred, and the numbers in each group which had to be withdrawn during the trial were recorded. At the end of the trial, a final assessment was made in each case, and a decision was taken as to whether clinical improvement warranted continuation of the drug. Records were kept of this decision and the dosage in each case.

RESULTS

The clinical progress made in each group when the inert tablets were being given is shown by the figures in Table I.

TABLE I

| Progress on Inert Tablets   |    |    |    | Pre-prochlorperazine<br>Group | Pre-chlorpromazine<br>Group |
|-----------------------------|----|----|----|-------------------------------|-----------------------------|
| Much improved .. .. .       | .. | .. | .. | 0                             | 0                           |
| Moderately improved .. .. . | .. | .. | .. | 0                             | 0                           |
| Slightly improved .. .. .   | .. | .. | .. | 2                             | 2                           |
| No change .. .. .           | .. | .. | .. | 23                            | 23                          |



The progress made when the active drugs were being given is shown in Table II.

TABLE II

| Progress on Active Tablets |    |    |    |    | Prochlorperazine<br>Group | Chlorpromazine<br>Group |
|----------------------------|----|----|----|----|---------------------------|-------------------------|
| Much improved              | .. | .. | .. | .. | 1                         | 1                       |
| Moderately improved        | .. | .. | .. | .. | 4                         | 1                       |
| Slightly improved          | .. | .. | .. | .. | 11                        | 17                      |
| No change                  | .. | .. | .. | .. | 9                         | 6                       |

In neither case is there any statistically significant difference between the two groups in regard to clinical progress.

The incidence of side effects is given in Table III. The totals (excluding drowsiness) of eleven for the prochlorperazine group and four for the chlorpromazine group show a difference significant at the 5 per cent. level. If Parkinsonism alone is taken, then the difference in the incidence in the two groups is significant at the 0.1 per cent. level.

TABLE III

| Side Effects                                                           |    |    |    |    | Prochlorperazine<br>Group | Chlorpromazine<br>Group |
|------------------------------------------------------------------------|----|----|----|----|---------------------------|-------------------------|
| <i>i. Parkinsonism</i>                                                 |    |    |    |    |                           |                         |
| Moderate                                                               | .. | .. | .. | .. | 8                         | 0                       |
| Slight                                                                 | .. | .. | .. | .. | 3                         | 1                       |
| Total                                                                  | .. | .. | .. | .. | 11                        | 1                       |
| <i>ii. Bizarre Positions</i>                                           |    |    |    |    |                           |                         |
| Total                                                                  | .. | .. | .. | .. | 1                         | 0                       |
| <i>iii. Jaundice</i>                                                   |    |    |    |    |                           |                         |
| Total                                                                  | .. | .. | .. | .. | 0                         | 1                       |
| <i>iv. Syncopal Attacks</i>                                            |    |    |    |    |                           |                         |
| Moderate                                                               | .. | .. | .. | .. | 0                         | 1                       |
| Slight                                                                 | .. | .. | .. | .. | 0                         | 1                       |
| Total                                                                  | .. | .. | .. | .. | 0                         | 2                       |
| <i>v. Abdominal Distension</i>                                         |    |    |    |    |                           |                         |
| Total                                                                  | .. | .. | .. | .. | 1                         | 0                       |
| <i>vi. Drowsiness</i>                                                  |    |    |    |    |                           |                         |
| Severe                                                                 | .. | .. | .. | .. | 2                         | 1                       |
| Moderate                                                               | .. | .. | .. | .. | 4                         | 3                       |
| Slight                                                                 | .. | .. | .. | .. | 11                        | 10                      |
| Total                                                                  | .. | .. | .. | .. | 17 (68%)                  | 14 (56%)                |
| <i>Totals in each group showing side effects other than drowsiness</i> |    |    |    |    |                           |                         |
| ..                                                                     | .. | .. | .. | .. | 11                        | 4                       |

In the group receiving prochlorperazine, one patient took up bizarre positions for a short time (not observed by the author) which seem to have been similar to those described by other workers. The symptom passed off spontaneously the dosage being maintained at 75 mg. daily. The same patient later developed Parkinsonism. The earliest feature of Parkinsonism most commonly noted was the immobility of the face, with resulting loss of expression, and occurred at dosages of prochlorperazine ranging from 75 to 150 mg. daily.

Shuffling gait was marked in some cases and cog-wheel rigidity was always present. Excess salivation with dribbling was rare. Tremor was marked only in a few cases, and when present was finer than is usually seen in Parkinsonism. In one of the cases showing Parkinsonism, unilateral rigidity of the flexibilitas cerea type occurred. The Parkinsonism in most cases responded to promethazine ("Phenergan") another phenothiazine derivative, in doses of 10 mg. t.d.s., but in several cases only partially. The effect of 10 mg. t.d.s. was found to be much superior to that of 25 mg. b.d. Another patient receiving prochlorperazine developed abdominal distension, which a consultant surgeon considered likely to be due to the drug. This symptom, which had followed the onset of Parkinsonism, did not respond to promethazine but subsided slowly on withdrawal of the prochlorperazine.

The case showing Parkinsonism whilst receiving chlorpromazine was not relieved by promethazine. The case of jaundice in the chlorpromazine group was of a moderately severe type with liver damage which was demonstrated by means of liver function tests (alkaline phosphatase 25 units per 100 ml., Van den Berg 3.0 mg./100 ml., serum protein 7.0G/100 ml., albumin 6.4 G and globulin 0.6 G.). One of the two cases of syncope in the chlorpromazine group was of minor degree and the other more severe, being accompanied by marked giddiness, necessitating withdrawal of the drug. A transient type of drowsiness was seen in a fairly large proportion of both groups, but in no way affected clinical progress. There was in fact no statistically significant difference in the incidence in the two groups. In two of the prochlorperazine group a moderate degree of restlessness occurred, although in neither case was it a disturbing feature. In one case it was transient, but in the other, who had some years previously been leucotomized, it proved more persistent.

TABLE IV

|                                   |                              | Prochlorperazine<br>Group | Chlorpromazine<br>Group |    |    |
|-----------------------------------|------------------------------|---------------------------|-------------------------|----|----|
| Numbers withdrawn during trial    | ..                           | 6                         | 2                       |    |    |
| Numbers continued at end of trial | ..                           | 11                        | 17                      |    |    |
| Dosages:                          |                              |                           |                         |    |    |
| Prochlorperazine group:           | Continued at 150 mg. daily   | ..                        | ..                      | .. | 9  |
|                                   | Continued at 112.5 mg. daily | ..                        | ..                      | .. | 1  |
|                                   | Continued at 75 mg. daily    | ..                        | ..                      | .. | 1  |
| Chlorpromazine group:             | Continued at 300 mg. daily   | ..                        | ..                      | .. | 16 |
|                                   | Continued at 150 mg. daily   | ..                        | ..                      | .. | 1  |

From Table IV it will be seen that the numbers withdrawn from the trial are six and two, for the prochlorperazine and chlorpromazine groups respectively. These figures show a difference only marginally significant (at the 20 per cent. level). At the end of the trial, when each patient was considered with regard to continuation of the drug, the decisions and dosages were as shown in Table IV. The dosage of prochlorperazine varied from 75 to 150 mg. daily, whilst that of chlorpromazine varied from 150 to 300 mg. daily.

#### DISCUSSION

The results of treatment with prochlorperazine would not, in the author's opinion, on the evidence obtained in this trial, justify the substitution of this drug for chlorpromazine, in the treatment of the aggressive, disturbed, chronic psychotic (especially schizophrenic) male patient. Particularly is this so in view

of the fact that there would seem a much greater expectation of side effects, especially Parkinsonism, with prochlorperazine.

There has been some suggestion amongst American workers that the best clinical results are obtained when Parkinsonism occurs. This hypothesis is not supported by the findings in this trial, the relevant figures being given in Table V.

TABLE V  
*Clinical Progress of Patients in Prochlorperazine Group Who Developed Parkinsonism (11) Compared with Those Who did not (14)*

|                        |    |    |    | 11 Patients Who<br>Developed<br>Parkinsonism | 14 Patients Who<br>did not Develop<br>Parkinsonism |
|------------------------|----|----|----|----------------------------------------------|----------------------------------------------------|
| Much improved ..       | .. | .. | .. | 0                                            | 1                                                  |
| Moderately improved .. | .. | .. | .. | 2                                            | 2                                                  |
| Slightly improved ..   | .. | .. | .. | 5                                            | 6                                                  |
| No change ..           | .. | .. | .. | 4                                            | 5                                                  |

It has also been suggested that the incidence of Parkinsonism might show a positive correlation with the amount of E.C.T. previously given. This hypothesis is not supported by the findings as shown in Table VI. In regard to these claims however, larger series would be required to allow definite conclusions to be drawn.

TABLE VI  
*Incidence of Parkinsonism in Prochlorperazine Group According to Groupings on Basis of Number of E.C.T. Previously Given*

|                                   |    |    |    | No E.C.T. | 1-10 | Over 10 |
|-----------------------------------|----|----|----|-----------|------|---------|
| Numbers of patients in each group |    |    |    | 15        | 6    | 4       |
| Parkinsonism:                     |    |    |    |           |      |         |
| Moderate ..                       | .. | .. | .. | 3         | 4    | 1       |
| Slight ..                         | .. | .. | .. | 3         | 0    | 0       |

On a purely clinical basis, reducing the dose of prochlorperazine when Parkinsonism occurred did not result in the improvement claimed by some American workers. Abdominal distension has been associated with prochlorperazine administration in the experience of French workers, and was considered by Delay, Deniker, Green and Mordret (1957), to be almost certainly due to spasm of the diaphragm. The clinical impression gained as a result of the weekly interviews during the trial, was that the two drugs were equally effective in the treatment of aggression, disturbance, and deterioration. In the treatment of the apathy found in the chronic schizophrenic patient, it was noted that chlorpromazine seemed very much superior to prochlorperazine. This effect of chlorpromazine on apathy was noted by Salisbury and Hare (1957).

From the experience gained in this trial it would seem that in psychiatric practice the dosage of prochlorperazine would be about half that of chlorpromazine. Table IV shows the doses given when the drugs were continued. The side effects of prochlorperazine, including Parkinsonism, which occurred in this trial, have been described and discussed by Delay *et al.* (1957), in a number of papers.

As originally planned it was intended that the trial should be over a longer period, and with reversal of the drugs received by the two groups. The high incidence of side effects in the prochlorperazine group led however to the curtailment of the trial.



## SUMMARY

An outline is given of the derivation, formula, and known pharmacology of prochlorperazine and of the use of chlorpromazine in the treatment of the aggressive, disturbed chronic psychotic patient. Fifty of this type of patient (mainly schizophrenic) were assessed and divided into paired groups. Inert tablets were given for two weeks, followed by increasing doses of prochlorperazine to one group and chlorpromazine to the other. The maximum doses were 150 mg. daily and 300 mg. daily respectively given for five weeks. Patients were interviewed at weekly intervals and a final assessment made. Side effects are described, especially marked being Parkinsonism in the prochlorperazine group.

The conclusion is reached that there is no advantage on clinical grounds in the use of prochlorperazine as opposed to chlorpromazine in the treatment of the aggressive disturbed chronic male psychotic, and that the greater incidence of side effects seems a contra-indication to its use in treating this type of patient. The dosage level of prochlorperazine would seem to be about half that of chlorpromazine in psychiatric practice.

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# THE USE OF PROCHLORPERAZINE (STEMETIL) IN CHRONIC PSYCHOTIC DISORDERS

By

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PROCHLORPERAZINE, 1-[3-(3-chloro-10-phenothiazinyl)propyl]-4-methyl-piperazine dimaleate, a phenothiazine derivative related to chlorpromazine, was discovered in the Rhône Poulenc laboratories, and studied pharmacologically in 1956, by Ducrot and Koetschet, for its anti-emetic properties. Clinical trials, following this experimental evidence, suggested that, as well as possessing powerful anti-emetic properties, the drug was of considerable therapeutic value in migraine, Ménière's syndrome, and vertigo of other origins.

Owing to an impression that the sedative effect of the drug was considerably below that of chlorpromazine, prochlorperazine was not employed, in its early stages, for psychiatric conditions in this country. Reports from abroad, however, indicated that it was proving of great value in mental hospital patients and might even replace chlorpromazine: at the same time, disturbing side-effects were observed when the dosage was increased to a level that was considered necessary for the treatment of psychiatric patients. In order to examine these claims, the trial reported in this communication was undertaken.

## METHOD

Prochlorperazine, in the form of 25 mg. tablets, was administered in doses of 1 tablet t.d.s. (75 mg. orally), in most cases until it became plain whether the drug was proving effective or not, or until side-effects necessitated withdrawal, reduction, or alteration of medication.

Patients who had been ill for a considerable time were selected so that they could act as their own controls for the trial. All these patients had received various forms of treatment, including insulin coma therapy, electroplexy, tranquillizers of the phenothiazine and Rauwolfia groups; and some had undergone prefrontal leucotomy, whilst others had been subjected to cardiazol convulsions many years before. No benefit had been obtained from any of these forms of therapy. (Later, when results from treatment of the chronic group became evident, a further small group of acutely ill patients was added to the trial.)

The group consisted of 13 male patients, with an average duration of illness of 13.4 years, and 46 females with an average duration of illness of 8.3 years.

Of the 13 male patients, 9 were hebephrenic, 1 was catatonic, 1 paranoid, and 2 were simple schizophrenics. Ten of these suffered from auditory hallucinations and delusions which dictated their behaviour and caused them to act in a violent, aggressive, impulsive way at times. The remaining 3 were the subjects of hypochondriacal delusions which inhibited any form of normal response or activity.

TABLE

|                                      | Number of Patients Treated | Average Age of Patient | Average Duration of illness | Number of Patients Previously Treated but Failed to respond |           |              |        |                | Average Daily Dose (mg.) | Results      |                      |                                   |                                         |
|--------------------------------------|----------------------------|------------------------|-----------------------------|-------------------------------------------------------------|-----------|--------------|--------|----------------|--------------------------|--------------|----------------------|-----------------------------------|-----------------------------------------|
|                                      |                            |                        |                             | Leucotomy                                                   | Cardiazol | Insulin S.T. | E.C.T. | Tranquillizers |                          | Not Improved | Improved in Hospital | Improved Home on Maintenance Dose | Recovered Home without Maintenance Dose |
| Schizophrenics:                      |                            |                        |                             |                                                             |           |              |        |                |                          |              |                      |                                   |                                         |
| Simple ..                            | 5                          | 44                     | 11.6                        | -                                                           | -         | 4            | 5      | 5              | 75                       | 3            | 2                    | -                                 | 1                                       |
| Catatonic ..                         | 2                          | 36                     | 9                           | -                                                           | -         | 2            | 2      | 2              | 75                       | -            | 1                    | -                                 | 1                                       |
| Hebephrenic ..                       | 27                         | 35.7                   | 15.9                        | -                                                           | 4         | 25           | 27     | 27             | 75                       | 6            | 12                   | 3                                 | 6                                       |
| Paranoid ..                          | 9                          | 46                     | 9.2                         | 1                                                           | 1         | 4            | 8      | 8              | 75                       | 2            | 2                    | 2                                 | 3                                       |
| Affective States:                    |                            |                        |                             |                                                             |           |              |        |                |                          |              |                      |                                   |                                         |
| Agitated depression ..               | 8                          | 52                     | 5                           | 1                                                           | -         | 3            | 8      | 8              | 75                       | 4            | 2                    | 1                                 | 1                                       |
| Mania ..                             | 5                          | 55                     | 32                          | -                                                           | -         | -            | 2      | 2              | 150                      | 1            | 2                    | -                                 | 2                                       |
| Reactive with neurotic depression .. | 3                          | 46                     | 6                           | -                                                           | -         | 3            | 3      | 3              | 75                       | 2            | 1                    | -                                 | -                                       |



Thirty of the female patients were schizophrenics, made up of 18 hebephrenics, 3 simple, 1 catatonic, and 8 paranoids, all presenting the same problems as were encountered with the males. The remaining 16 females were suffering from severe agitation of long standing or manic depressive psychoses, the average duration of their illnesses being  $5\frac{1}{2}$  years.

### RESULTS

Improvement in the patients, if improvement there was to be, became apparent within the first 48 hours of treatment. The beneficial effect of the drug showed itself in the form of cessation of aggressive and violent behaviour, the patients no longer acting at the command of their delusions or hallucinations. They were enabled to react adequately to their surroundings and to behave amiably towards their fellow patients, relatives, and the nursing staff. This was in complete contradiction to their previous attitude of absolute hostility of many years standing, often carried to the length of violent assaults. Hallucinatory experiences were no longer reported by the patients and independent observation did not reveal any evidence of their presence. Delusions were no longer voiced and enquiry of the patients concerning such manifestations was dismissed or shrugged off as being of no consequence. Concurrently with these improvements, the patients became able and willing to take part in ward activities, attend occupational therapy, and visit their homes for the first time in many years. Furthermore, those patients who previously had been faulty or neglectful in their habits were now able and anxious to attend to their own needs, with the result that their appearance and physical state improved markedly.

Five patients, who had been very disordered in every respect, improved to such an extent that they developed actual insight into the psychogenic origin of their illnesses. This was the more remarkable because these five had been ill for well over 10 years and had, during the whole period of their illnesses, been quite unable to discuss their problems with any suggestion of insight.

The change in patients who responded appeared gradually, and it was impossible to predict at what stage, both as regards dosage and period of administration, maximum improvement might be expected in individual cases; so, as an empirical measure after a period varying between 30 and 150 days of treatment, dosage was halved. A small number of patients soon relapsed and only regained their improvement after dosage was restored to a single dose of 75 mg. daily, but the majority maintained or continued their improvement on half this dosage.

All improvements mentioned took place in patients in whom delusions and hallucinations were prominent features. Those patients whose symptoms were less spectacular, and whose behaviour was only mildly disturbed, exhibited little or no benefit from the administration of prochlorperazine. Furthermore, agitated depressives showed no response, although they were helped by chlorpromazine. Manic-depressives, in the manical phase, were also disappointing. A dosage of up to 200 mg. per day was necessary to control their excitement, but, even at that level improvement was not maintained, and remissions could only be obtained by employing other forms of physical treatment.

Of the responsive group, however, a number (21) continued to improve after prochlorperazine was withdrawn, and were able to return to their homes and to make the necessary social adjustments incumbent upon such a change in environment and responsibility.

## ILLUSTRATIVE CASES

*N.T.*, single female, aet 37, who had been suffering from schizophrenia for 4 years. Her condition fluctuated between catatonic stupor with *flexibilitas cerea* and cyanotic extremities, and periods of psychotic excitement during which she frequently smashed windows and crockery. She had previously been treated with insulin coma therapy on 2 occasions, had received repeated courses of electroplexy, and had been given tranquilizers or sodium amylal without any signs of improvement.

When she started on prochlorperazine she was in a catatonic stupor. Within a remarkably short time she improved, became active, co-operative and pleasant, joined in the ward activities, and was soon able to go home for weekends. Her physical state improved and the cyanosis of her extremities disappeared. After 3 months on 75 mg. prochlorperazine daily, she became tearful, developed a tic affecting her arms and shoulders. At her request the tablets were discontinued. The tic was regarded as being of psychogenic origin rather than a side-effect of the drug, and soon afterwards she developed insight into the origin of her illness when her tic was regarded as "throwing up her arms in despair" at the hopelessness of ever achieving satisfactory relationships in the face of emotional blackmail from her stepmother. She is now well able to cope with these emotional difficulties.

*A.P.D.*, a single male, aet 34, had suffered from hebephrenic schizophrenia for 10 years. His behaviour was frequently disturbed as the result of insulting auditory hallucinations and persecutory delusions. He made frequent attacks on other patients and the nursing staff; smashed many windows, neglected himself, and was never accessible to ordinary reasoning.

After the failure of insulin coma therapy, electroplexy, and a prolonged course of chlorpromazine, prochlorperazine was started at a daily dosage of 75 mg. and within a short time, his violent, unco-operative, disturbed behaviour disappeared. No longer did he respond to auditory hallucinations, nor did he feel persecuted. He became tidy, clean and helpful, rational conversation became possible, and he was able to enjoy every freedom within the hospital. The improvement continued after the dose of prochlorperazine was halved and he is soon to attend the rehabilitation centre.

## SIDE EFFECTS

*Parkinsonism.* The most alarming side-effect experienced during the administration of prochlorperazine was a Parkinsonism-like state. This was heralded by muscle twitchings, pallor, lethargy, and complaints of tightness in the chest, and progressed towards complete muscular rigidity with excessive tonus, tremor, and painful muscular distortions. The time of onset varied between 3 and 90 days. The condition disappeared soon after withdrawal of the drug, and it was observed that mental improvement was maintained during and after such an episode. So soon as the condition had disappeared, it was found that there was no recurrence when prochlorperazine was re-started, at the same dose, if administered together with 25 mg. promethazine, dose for dose, and, if anything, with enhanced benefit to the mental condition.

*Skin.* One patient developed a skin reaction, similar to that seen with chlorpromazine, which disappeared two days after withdrawal of the drug.

*Vasomotor symptoms.* Four patients displayed vasomotor symptoms resembling peripheral vascular collapse. Prochlorperazine was withdrawn immediately and the patients quickly recovered. All 4 patients were re-started on the drug, at a lower dosage,  $12\frac{1}{2}$  mg. t.d.s., which was gradually increased without the appearance of further symptoms.

*Drowsiness.* Three patients became drowsy after 2 days on 75 mg. per day. Dosage was halved and there was no further complaint.

*Excitement.* One patient felt that prochlorperazine increased excitement and asked for the drug to be stopped. The drug was withdrawn and the excitement subsided.

Three schizophrenics, who had shown partial remissions through the administration of prochlorperazine, asked for the drug to be stopped as they believed that it was the cause of their disease. When the drug was withdrawn they continued to improve and soon became symptom free.

## DISCUSSION

Prochlorperazine is one of many phenothiazine derivatives and, as such, shares pharmacological properties to a varying degree with other compounds. Because of this, a trial and a report concerning it would be of little value unless one of these properties was so outstanding as to render prochlorperazine more efficacious than other compounds in any particular disorder.

This trial confirmed that prochlorperazine was more effective than chlorpromazine in the control of certain severe psychotic symptoms. Its main benefit was found to be in patients whose behaviour was severely disturbed as the result of persistent hallucinations and delusions.

Patients with excessive psychomotor activity, who were usually over-active, hostile, and aggressive, obtained maximum benefit from the drug. Those who showed only thought disorder, without abnormal psychomotor behaviour, did less well or failed to benefit at all.

It is of interest that the nature of the side-effects suggested that the toxic action of the drug was exerted on those parts of the brain which are concerned with motor activity; the symptoms being those commonly associated with irritative lesions of the basal ganglia as found in Parkinsonism. From this it might be tentatively deduced that prochlorperazine acts on the brain stem, the basal ganglia in particular. If the argument be continued further, it may be suggested that the beneficial effect of the drug, in patients with abnormal psychomotor activity, is primarily due to its action on the primitive motor ganglia.

Many clinicians are, however, directly opposed to the assumption that abnormal psychomotor activity is the primary disorder. The latter is usually regarded as an expression of a disorder of thinking and abnormal perspective, and, that so long as disordered thoughts exist, disorder of motor activity results. On this premise, disorder of thinking is the primary symptom, and disorder of behaviour the secondary, in which case, as the action of prochlorperazine is primarily on the secondary symptoms, it remains to be explained how and why those primary symptoms remit during administration of the drug.

The results of this trial indicate that prochlorperazine is mainly effective in severely disturbed, chronic patients; and, therefore, has its main place in mental hospitals: little or no indications for its use in psychiatric out-patients or in general practice could be found. The side-effects are of a nature to cause alarm to the patient and his relatives and they provide additional reasons why the drug should be restricted to selected patients undergoing hospital treatment, and those for whom the necessary maintenance dose has been determined in hospital.

## SUMMARY

The effect of prochlorperazine on psychiatric patients has been investigated and found to be of value in the treatment of severely disturbed schizophrenics. It was found to be of little use in other psychiatric conditions.

The main side-effect was a type of Parkinsonism which provoked alarm in the patient and those around him. This disappeared on withdrawal of the drug or when promethazine was administered concurrently.

Prochlorperazine in doses effective for psychiatric conditions should be employed mainly in mental hospitals.

(Prochlorperazine, under the trade mark of "Stemetil", was provided by May & Baker, Dagenham.)

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# STELAZINE (TRIFLUOPERAZINE) A PRELIMINARY REPORT ON A CLINICAL TRIAL

By

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TRIFLUOPERAZINE, which is 2-trifluoromethyl-10-(3'-[1"-methylpiperazinyl-4"-propyl)-phenothiazine dihydrochloride—a preparation manufactured by Smith, Kline and French Laboratories Limited under the description SKF5019—is the most recent phenothiazine derivative reported to have a beneficial effect on certain types of mental illness. On the basis of animal tests trifluoperazine is described as having nine times the potency of chlorpromazine in blocking the conditioned response, and its specificity is greater than that of chlorpromazine.

Sixty patients were selected for this trial (40 females whose ages ranged from 20–72 years, the average being 42, and 20 males whose ages ranged from 24–50 years, the average being 38). The majority were chronic schizophrenics and the duration of their psychiatric illness averaged 11 years for females, ranging from 1–32 years, and 7 years for males, ranging from 2–14 years. They had failed to respond to the normally recognized forms of treatment. Many were of the disturbed hallucinated impulsive type whose prognosis was regarded as hopeless. Such long-stay patients constitute a problem in every mental hospital and their treatment by a new drug presents the severest test of its efficacy.

Trifluoperazine was given by mouth in capsule form. The initial dose was 5 mg. a day for three days. This was increased at intervals of three days to 5 mg. b.d. and 5 mg. t.d.s. and by 5 mg. steps to 10 mg. t.d.s. The maximum dose tried was 40 mg. a day. The usual maintenance dose in men was 25 mg. and in women 15 mg. a day. All patients had a maximum dose of 10 mg. t.d.s. except where toxic symptoms necessitated a reduction. Once stabilized on the appropriate dose, a double blind technique was introduced unknown to the nursing staff. Half of the patients were kept on Trifluoperazine and half were given a placebo which was identical in appearance with the drug. The choice of patients was determined solely by the pharmacist.

The results of the double blind technique will be the subject of a further communication.

The results of treatment were determined qualitatively with particular emphasis on such clinical observations as the lessening in activity of hallucinations and of aggressive conduct; and the emergence of alertness, interest, initiative, etc.

All patients showing improvement were ranked according to estimated degree of improvement and a rank order produced for the females and males separately. From this the following figures were obtained:

TABLE I

| Improvement | Males  |            | Females |            | Mean Percentage |
|-------------|--------|------------|---------|------------|-----------------|
|             | Number | Percentage | Number  | Percentage |                 |
| Marked ..   | 6      | 30         | 7       | 17.5       | 23.75           |
| Moderate .. | 6      | 30         | 16      | 40         | 35              |
| Slight ..   | 3      | 15         | 11      | 27.5       | 21.25           |
| None ..     | 5      | 25         | 6       | 15         | 20              |

The figures for improvement were then broken down as follows. Table II shows the effect on symptoms.

TABLE II

|                                 | Number of Patients |    | Much Improved | Moderately Improved | Slightly Improved | No Change |
|---------------------------------|--------------------|----|---------------|---------------------|-------------------|-----------|
| Hallucinations ..               | 50                 | 18 | 14            | 9                   | 9                 |           |
| Aggression and noisiness ..     | 48                 | 20 | 13            | 7                   | 8                 |           |
| Withdrawal from surroundings .. | 23                 | 9  | 8             | 2                   | 4                 |           |
| Thought disorder ..             | 32                 | 11 | 13            | 2                   | 6                 |           |

Table III shows the effect on behaviour.

TABLE III

|                |    |    |    | Before Treatment<br>Number of Patients | After Treatment<br>Number of Patients |
|----------------|----|----|----|----------------------------------------|---------------------------------------|
| Spontaneity .. | .. | .. | .. | 13                                     | 42                                    |
| Sociability .. | .. | .. | .. | 3                                      | 38                                    |
| Speech ..      | .. | .. | .. | 24                                     | 46                                    |
| Occupation ..  | .. | .. | .. | 11                                     | 40                                    |

#### COMMENTS

Improvement became noticeable approximately ten days after commencement of treatment. This was most striking in the fading of hallucinations, cessation of impulsiveness, an awakening of interest, a desire to take part in occupations and recreations of various kinds. It was also noted that many patients were moderately euphoric, in some appetite was increased, and a few became aware of their previous irrational conduct.

#### PSYCHOMETRIC INVESTIGATION

Clinical observations of the effect of trifluoperazine indicated changes in motor activity and general awareness in a small sample of patients.

From this evidence it was decided to measure quantitative changes in motor speed, hand-eye co-ordination and attention level.

The battery of tests used in the investigation were:

1. Modified Peg Board test of motor speed (3 trials).
2. Bead-threading test of co-ordination (3 trials).
3. Knox Cube test of attention level.

All three tests lend themselves to rapid individual administration and are sufficiently simple to be relatively unaffected by variations in intellectual level.

The battery was given to each patient a day or two before treatment commenced with a repeated administration three weeks later.

Differences between mean scores obtained on each test before and during treatment proved to be significant in the case of speed and attention tests for both men and women (see Table IV).

TABLE IV  
*Significance of Difference Between Means of Tests Before and During Treatment in Terms of Units of P.E. Difference*

| Test          | Men (N=18)           |    |    |     | Women (N=26)         |    |    |     |
|---------------|----------------------|----|----|-----|----------------------|----|----|-----|
|               | × P.E. of Difference |    |    |     | × P.E. of Difference |    |    |     |
| Co-ordination | ..                   | .. | .. | 2.7 | ..                   | .. | .. | 2.3 |
| Speed         | ..                   | .. | .. | 4.7 | ..                   | .. | .. | 4.9 |
| Attention     | ..                   | .. | .. | 8.2 | ..                   | .. | .. | 7.2 |

A similar comparison of coefficients of variation for the co-ordination and speed tests revealed a significant difference only in the case of the speed test (3.7 P.E. for men and 3.5 P.E. for women). The coefficient of variation yields in this case a measure of uniformity of performance over the three trials of each of these tests.

From the results to hand, the following changes have been observed during the period of treatment in both male and female groups:

1. A significant increase in speed of performance on the peg-board test.
2. A significant increase in the score on the Knox Cube attention level test.
3. A significant decrease in the scatter of speed over three trials of the peg-board test, i.e. a significantly more uniform performance on this motor speed test.

Further investigation is being carried out to exclude the possible effects of learning and environmental changes.

SIDE EFFECTS

These were noted in 28 patients (46.5 per cent.) of which 11 were males and 17 females.

The following occurred:

- I. Parkinson-like symptoms:
- (a) Mask-like face.
  - (b) Tremors.
  - (c) Muscle pains.
  - (d) General rigidity.
  - (e) Bent shoulders and shuffling gait.

In only 8 cases (13.23 per cent.) were these symptoms severe; the rest, 16 cases (26.6 per cent.) were of a mild character.

Other side effects were:

- |                 |        |           |
|-----------------|--------|-----------|
| II. Drowsiness  | Male=1 | Female=5. |
| III. Salivation | Male=0 | Female=6. |



|                  |        |           |
|------------------|--------|-----------|
| IV. Restlessness | Male=0 | Female=1. |
| V. Lachrymation  | Male=0 | Female=2. |
| VI. Sweating     | Male=0 | Female=1. |

Of these cases, side effects appeared between seven to thirty-two days after commencement of treatment, usually after twenty-one days. The dosage at the time of appearance of most side effects was 30 mg. per day, but a few cases occurred at a lower dosage, the lowest being 15 mg. per day. In eight cases all side effects disappeared on reduction of dose from 30 to 20 mg. per day. In three patients in whom it was necessary to stop treatment, resumption of treatment at a smaller dose (15 mg. per day) did not cause a re-appearance of side effects. In one case reduction of dose was combined with 2 mg. Artane b.d. but in the main alteration of dose only was effective. The beneficial effects of a reduction of dose was noted in 48 hours. In only two cases (female) was permanent cessation of treatment necessary for the abolition of Parkinsonism.

Other investigations showed that the blood pressure readings were unaffected, that in general there was a slight leucocytosis, and there were no cases of jaundice or urinary complications.

#### DISCUSSION

The results so far obtained show that trifluoperazine is a powerful drug which has considerable beneficial effect when given to chronic psychotic patients. Although side effects are fairly numerous, the majority were overcome in general by reduction of dosage, and specific symptoms by their appropriate antidote. In some cases in which it was necessary to withdraw the drug completely, the improvement that had already taken place in the patients' condition was maintained for at least several weeks although, conversely, a patient who was discharged against advice while on 10 mg. t.d.s. relapsed and was back in hospital within ten days.

Concerning the site of action of Trifluoperazine, the sweating, lachrymation, salivation and drowsiness noticed in some patients suggest to us that one site might be the middle group of hypothalamic nuclei and likewise the interruption of the extra-pyramidal facilitatory pathway in the hypothalamus might account in part at least for some of the signs of Parkinsonism.

Our preliminary conclusions support the findings of Rudy *et al.* (1) and we feel that further research will reveal that Trifluoperazine will prove a great therapeutic advance in the treatment of mental disorders.

#### SUMMARY

Sixty chronic psychotic patients were selected for this clinical trial. Observation showed that a high proportion were improved by Trifluoperazine.

The presence and control of side effects are discussed, as are the results of a parallel psychometric investigation.

#### ACKNOWLEDGMENTS

We are indebted to Dr. A. B. Monro, Physician Superintendent, for permission to carry out this survey at Long Grove Hospital, Epsom, to Dr. A. Hall Ratcliffe for his suggestions and criticisms, and to Messrs. Smith, Kline and French for their generous supply of trifluoperazine and placebos.

We are grateful to Mr. A. Fann, Pharmacist, and to the nursing staff of Long Grove Hospital, Epsom, for their co-operation.

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# THE EFFECTS OF PROMAZINE ("SPARINE") IN CHRONIC SCHIZOPHRENIA

By

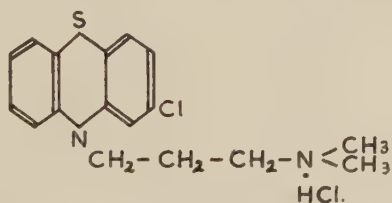
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and

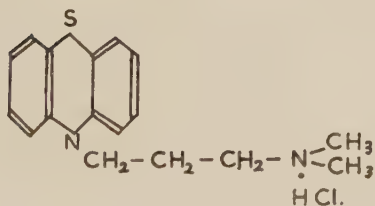
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PROMAZINE hydrochloride ("Sparine") is a phenothiazine derivative which has recently been introduced to this country with claims to be a "tranquillizing" drug. It is closely related chemically to chlorpromazine but does not contain the chlorine atom which has been thought to cause the undesirable side effects of the promazine group. The structural formula of Sparine compares with that of chlorpromazine as follows:



Chlorpromazine Hydrochloride.



Promazine Hydrochloride (Sparine).

Most of the published work on Sparine has been carried out in the United States of America where it has been reputed to be effective in the management of acute agitation and confusion such as may occur in patients with schizophrenia, manic states, senility, or childhood behaviour disorders and in the management of acute alcoholism and drug addiction.

American workers regarded promazine as particularly useful in the acutely agitated patient because the onset of its action was immediate when given intravenously or intramuscularly, and it brought the patient under control rapidly and effectively. In many patients, the intravenous administration of small doses rapidly induced a preliminary state of somnolence. This state was usually of comparable duration to normal physiological sleep, but it was a

form of sleep from which, even at its deepest, the patient could be roused easily, without any of the residual confusion or clouding of consciousness that is so common a feature of barbiturate sedation.

Fazekas and his colleagues (1956) found Sparine effective in controlling the hyperactivity in manic-depressive psychotics and in agitated schizophrenics with an initial intravenous dose of 50 to 200 mg. and a maintenance dose of 100 to 200 mg. every 4 to 6 hours orally, intramuscularly or intravenously. Sparine did not appear to correct the underlying psychological disturbance in such patients. Thus, hallucinations were not abolished but after treatment became less intense and troublesome and the patients appeared unconcerned by them.

Fazekas also found promazine valuable in the treatment of acute hallucinosis and delirium tremens and Mitchell (1956) has reported highly satisfactory results with the drug in the relief of withdrawal symptoms in chronic alcoholic patients.

Freed (1955) reported that Sparine controlled rapidly and effectively the symptoms of central nervous system excitation. Usdin (1956) stated that the cardinal use of promazine to date seemed to be in the treatment of senile agitation and of drug and alcoholic addiction, although also of definite value in other conditions.

There would seem to be little or no work published as yet on the effects of promazine hydrochloride on the more chronic mental conditions. The purpose of this investigation was to study the effects of the drug on a group of chronic schizophrenic patients.

#### MATERIAL AND METHOD

Forty-six patients (33 female and 13 male) were given Sparine orally. They all suffered from a chronic schizophrenic illness, three being basically oligophrenic in addition. Their present stay in hospital ranged from 1 to 37 years with an average of 16 years. Ages ranged from 27 to 71 with an average of 47 years. The majority had previously had some form of physical treatment; 8 had undergone prefrontal leucotomy. The case material was therefore the least promising available, as all the patients were suffering from a very chronic illness and many showed a deterioration. However, a considerable number of this group when previously treated by other tranquillizing drugs had shown a minimal or temporary improvement.

Treatment was commenced with 150 mg. daily for one week, then it was increased to 300 mg. daily for a further two weeks after which a dose of 600 mg. was maintained for five weeks. The drug was administered in a divided dosage three times daily. For the final three weeks of the investigation placebo tablets identical in appearance to the active drug were given. The full course of treatment thus occupied thirteen weeks.

#### RESULTS

The individual results were assessed by ourselves with the assistance of the Sisters or Charge Nurses who were in daily contact with the patients. The nursing staff have now had considerable experience in this hospital in co-operating in the investigation of the effects of new drugs.

Table I summarizes the results of the treatment. Six patients (13 per cent.) benefited from the drug, thirty-five (76 per cent.) showed no significant change and five (11 per cent.) became worse. Three patients who had previously been



quieter, less aggressive and more co-operative on chlorpromazine, whilst showing no further change on Sparine, maintained their original improvement. Of the six patients who showed some improvement, only two deteriorated on the placebo and all the five patients whose condition became worse remained so with the placebo.

TABLE I  
*General Results of Treatment with Sparine*

|               |    |    |    | Female | Male | Total    |
|---------------|----|----|----|--------|------|----------|
| Much improved | .. | .. | .. | 0      | 0    | 0        |
| Improved      | .. | .. | .. | 4      | 2    | 6 (13%)  |
| No change     | .. | .. | .. | 26     | 9    | 35 (76%) |
| Worse         | .. | .. | .. | 3      | 2    | 5 (11%)  |
| Much worse    | .. | .. | .. | 0      | 0    | 0        |
|               |    |    |    | 33     | 13   | 46       |

Table II shows a more detailed analysis of the effects of Sparine on various signs and symptoms. It will be seen that Sparine had little significant effect on any of these. Aggression was improved in eight patients (21 per cent.), but it could only be said to have been abolished in one case and in the other seven the diminution in its intensity could not be considered striking.

TABLE II  
*Analysis of the Effects of Sparine on Certain Signs and Symptoms*

| Symptoms and Signs | Present at Onset | Improved | No Change | Worse |
|--------------------|------------------|----------|-----------|-------|
| Aggression         | 38               | 8        | 28        | 2     |
| Delusions          | 36               | 3        | 32        | 1     |
| Hallucinations     | 41               | 1        | 38        | 2     |
| Severe withdrawal  | 18               | 3        | 13        | 2     |
| Retardation        | 21               | 4        | 15        | 2     |
| Overactivity       | 12               | 2        | 9         | 1*    |
| Depression         | 5                | 2        | 2         | 1     |
| Tension            | 14               | 3        | 9         | 2     |
| Elation            | 5                | 0        | 4         | 1     |
| Confusion          | 30               | 2        | 25        | 3     |
| Impulsiveness      | 38               | 4        | 32        | 2     |
| Faulty habits      | 9                | 0        | 9         | 0     |

\* An additional two patients who had not previously shown overactive tendencies became overactive.

There was an average increase in the pulse rate of five beats per minute. In 32 patients, the pulse became faster during treatment and in 11 patients it became slower. There was no significant change in weight or in the systolic and diastolic blood pressures.

#### TOXIC AND SIDE EFFECTS

Reported side effects following the short term use of Sparine have been few and not serious in nature or degree. Transient postural hypotension has been noted in a few patients usually following the first parenteral injection. When this happened recovery was spontaneous and the symptoms of weakness and dizziness disappeared. Allergic skin reactions, hepatic dysfunction and extrapyramidal symptoms resembling Parkinson's syndrome have not been observed in patients receiving Sparine. One case of agranulocytosis associated with

Sparine therapy has been reported. This patient was on a very large dosage and recovered after the drug was stopped and appropriate treatment given. Sparine treatment was subsequently resumed in reduced dosage and after a period of three months there was no further evidence of haematopoietic depression.

In our series of patients no toxic or side effects were encountered. One patient who was receiving the drug died but it was not considered that Sparine was an attributable or aggravating factor in the death. This was a female patient aged 72 years, who developed a temperature and was found to have a pneumonic condition of both lungs. Sparine was stopped and she was given antibiotics with initial improvement but a week later she became comatose and died after 24 hours. A post-mortem examination revealed a broncho-pneumonia in both lower lobes, a flabby myocardium and atheroma. There was no evidence of agranulocytosis in this case.

#### SUMMARY AND CONCLUSIONS

1. The effects of a new tranquillizing drug Sparine (Promazine) on forty-six chronic schizophrenic patients are described.
2. This drug has been reported to be particularly useful in the treatment of acute agitation and confusion, acute alcoholism and drug addiction.
3. Sparine was found to be of no value in the treatment of this series of chronic schizophrenic patients. Thirteen per cent. of the patients benefited to a limited extent from the drug, 11 per cent. became worse and 76 per cent. showed no change.

#### ACKNOWLEDGMENTS

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# GENERAL PARESIS COMPLICATING HUNTINGTON'S CHOREA

By

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THAT chorea may sometimes occur as a result of cerebral syphilis has been accepted for some years (Kinnier Wilson 1940) and it has often previously been reported in association with G.P.I. The literature on the topic is dealt with by Lowrey and Smith (1918), Stone and Falstein (1938) and Weickhardt (1945). In all the reports however I can find only three previous instances where clinical and serological evidence of G.P.I. in a patient was associated with a family history and clinical syndrome of Huntington's chorea. These cases were reported by Pagliano and Avierinos (1922), Urechia and Rusdea (1922) and Stone and Falstein (1938) and the case here described appears to be only the fourth similar example to be reported. It has a practical as well as an academic interest since the differential diagnosis of the early stages of Huntington's chorea from those of G.P.I. is still sometimes necessary.

## CASE HISTORY

C.E. Housewife. First admitted to hospital in 1942, aged 34 years. Her father died in a mental hospital aged 38 years. He was said to have the physical signs of G.P.I. and no particular evidence of chorea was recorded in his case. Her brother, J. McA., is now a patient in Cherry Knowle Hospital. He has shown a personality change since 1939 and is now demented and subject to choreic motor disorder and involuntary movements. He shows no signs of syphilis and his cerebrospinal fluid is normal as well as his blood Wassermann reaction and Kahn test.

The patient herself had been "not well" for four years prior to her admission to hospital in 1942. She had been a poor scholar and always illiterate but cared for her four children until she developed headaches and inability to walk, diagnosed at a general hospital as neurotic. At the time of first admission she was obese and infected with scabies. The pupillary reflexes were normal and there was no abnormality recorded in the central nervous system except "pseudo-clonus" at the right ankle and a mild symmetrical increase in the tendon-reflexes in the legs. The record of the Wassermann reaction in the blood has been lost but it was negative in the cerebrospinal fluid. The Lange colloidal gold curve read 2221110000. She was then regarded as basically feeble-minded with hysterical and schizoid features. She was dull, quarrelsome and not very clean but worked and occupied herself when given clear instructions.

She was re-admitted to hospital in 1943 in a similar state, being then depressed and tremulous as well, and she remained in hospital from that time. In 1947 she was still able to occupy herself in the laundry but she had some ataxia and fell unduly often. Her pupils by then were irregular and unequal and did not react to light, her speech was slurred, tendon reflexes were increased in the legs and there was bilateral ankle clonus with flexor plantar responses. The Wassermann reaction in the cerebrospinal fluid was strongly positive and the Lange curve read 5554321000. She then received 5 intramuscular injections of a bismuth preparation and a course of 5 megaunits of penicillin. In the two months subsequently she showed little change but an inoculation with malarial blood was then successful in producing rigors and she experienced twelve bouts of pyrexia exceeding 103°F. The rigors were terminated effectively with quinine and she appeared more settled. Although jerky in her movements her ataxia was improved but she remained untidy and dishevelled and liable to snatch food from other patients.

In March 1949, six months after the last observations and nine months after ceasing malarial treatment, she appeared worse. She was confused and staggering and had much coarse tremor of her arms. In 1950 she was demented and in need of constant nursing supervision and showed jerky spastic movements. In 1951 weakness of the facial muscles, particularly levator palpebrae, was recorded together with "trombone



tongue", ataxic gait and flexor plantar responses. In March 1952 the dementia and physical deterioration were still progressing and she was inaccessible to conversation; she was also very restless and the presence of choreiform movements was recorded in the case-notes.

In May 1952 she received 1,800,000 units of crystalline penicillin and a further 2,000,000 units of "Distaquine" penicillin for the treatment of a cutaneous infection but her movements continued to be severe until her death after increasing enfeeblement in December of that year. The death was certified at the time as due to General Paralysis.

#### COMMENT

A re-appraisal of this case was only made some time after her death and following on the diagnosis of Huntington's chorea in her brother. Even allowing for her poor original intelligence, however, it is clear that there was clinical evidence of mental and physical changes developing at a time when the Wassermann reaction in the spinal fluid was negative and this evidence together with the onset of her first symptoms at the age of thirty and the long course of her illness supports the additional diagnosis of Huntington's chorea in her case. Further when the signs of syphilis were established she received treatment which seems to have affected the progress of the tertiary infection and even appeared to produce some temporary improvement. Subsequently, however, an increasing dementia again became manifest together with progressively more numerous jerky movements until finally the choreic signs were the predominant ones, and this chorea continued to become worse despite coincidental treatment with a second course of penicillin. It is likely therefore that Huntington's chorea was the cause of her presenting symptoms and of her ultimate physical disabilities and we may reasonably suppose that some of the changes of G.P.I. were superimposed upon the Huntingtonian syndrome. Such a conclusion emphasizes the importance of the serological examinations for syphilis in chronic chorea even where a confirmed family history of Huntington's chorea is to be found.

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# PERSISTENT PSYCHIATRIC DISORDERS AFTER HEAD INJURIES IN CHILDREN

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## INTRODUCTION

HEAD injuries in children have been studied less extensively than those in adults, in particular, their psychiatric aspects. Ssouchareva and Einhorn (1935), Blau (1936), Riggenbach (1946), Fabian and Bender (1947), Lutz (1951) and others have given special attention to such aspects. However, there are still marked discrepancies in the assessment of the various aetiological factors and their prognostic importance in determining prolonged psychiatric sequelae.

Ssouchareva and Einhorn found that 16 out of a group of 30 children showed disturbances more than a year after the injury. Lutz stressed the serious prognosis of head injury in children, for he found that out of his own material of 24 cases and a review of other published cases, 10 per cent. showed permanent symptoms. This percentage comprises both neurological and psychiatric disturbances. On the other hand, Riggenbach followed up 167 cases of head injury in children, and found only 6 with lasting psychiatric symptoms.

The selection of cases may account for the conflicting findings, for 42 per cent. of Ssouchareva's cases were said to have behaviour disturbances or intellectual defect before the injury, while Riggenbach's were chosen from a group of children referred to a surgical clinic after head injury. It is unlikely that the latter group contained more than an average number with psychiatric symptoms before the injury. Lutz selected his cases from both surgical and psychiatric clinic sources.

In a preliminary study of head-injured children selected from patients of the Children's Department of the Maudsley Hospital, it appeared that the injury itself was not the most important factor in many cases of persistent psychiatric disability. To confirm this impression, it was decided to examine and follow up a larger sample of children seen at this psychiatric centre and to compare them with another sample of children previously admitted to surgical wards with head injury and subsequently followed up for psychiatric sequelae.

All the records of children seen between the years 1947 and 1955 at the Children's Department of the Maudsley Hospital were examined for a history of head injury. Similarly the records of children admitted after head injury to the Casualty Ward of University College, London, and the Accident Hospital in Birmingham between the years 1946-1955 were inspected. Only

those cases that had sustained a severe head injury were included in the investigations. The criteria of severity were: a definite period of loss of consciousness, radiological evidence of skull fracture, transitory or permanent neurological sequelae. Any one of these criteria was considered sufficient for inclusion in either group.

All the children were personally examined for the purpose of this investigation and at least one of the parents interviewed.

The limited information on the immediate psychiatric effects of head injury in these cases made it necessary to limit this study to the long-term sequelae.

### FINDINGS

Table I shows that there were 31 "psychiatric clinic cases" and 32 "surgical clinic cases" and that boys were much more prone to head injuries in both series.

TABLE I  
*Age, Sex Distribution and Cause of Accident*

|                      |    |    |    |    | Psychiatric<br>Clinic Cases | Surgical<br>Clinic Cases | Total |
|----------------------|----|----|----|----|-----------------------------|--------------------------|-------|
| Males ..             | .. | .. | .. | .. | 25                          | 23                       | 48    |
| Females ..           | .. | .. | .. | .. | 6                           | 9                        | 15    |
| Total ..             | .. | .. | .. | .. | 31                          | 32                       | 63    |
| Age at Head Injury:  |    |    |    |    |                             |                          |       |
| Under 4 years        | .. | .. | .. | .. | 5                           | 4                        | 9     |
| 4 years ..           | .. | .. | .. | .. | 4                           | 2                        | 6     |
| 5 years ..           | .. | .. | .. | .. | 8                           | 8                        | 16    |
| 6 years ..           | .. | .. | .. | .. | 7                           | 7                        | 14    |
| 7 years ..           | .. | .. | .. | .. | 1                           | 2                        | 3     |
| 8 years ..           | .. | .. | .. | .. | 4                           | 5                        | 9     |
| 9 years ..           | .. | .. | .. | .. | 2                           | 2                        | 4     |
| 10 years and over .. | .. | .. | .. | .. | 4                           | 3                        | 7     |
| Total ..             | .. | .. | .. | .. | 35*                         | 33*                      | 68    |
| Cause of Accident:   |    |    |    |    |                             |                          |       |
| Road accident ..     | .. | .. | .. | .. | 17                          | 13                       | 30    |
| Fall from height ..  | .. | .. | .. | .. | 11                          | 11                       | 22    |
| Simple fall ..       | .. | .. | .. | .. | 5                           | 5                        | 10    |
| Blow ..              | .. | .. | .. | .. | 2                           | —                        | 2     |
| Not known ..         | .. | .. | .. | .. | —                           | 4                        | 4     |
| Total ..             | .. | .. | .. | .. | 35*                         | 33*                      | 68    |

\* 5 children sustained more than one head injury and are tabulated accordingly.

In the *psychiatric clinic group*\* 16 were referred for symptoms thought to be related to the head injury, while 13 were referred for behaviour disorders, and it was in the course of investigation that a history of head injury emerged. Two cases were already on the waiting list for child guidance treatment when the injury occurred. Three children were first seen within three months of the head injury; 7 between three months and a year; 4 during the second year and the remainder at variable periods up to eight years after the accident. Many of these cases were under treatment for prolonged periods and were followed up for several years.

\* Refers to cases seen at Children's Department, Maudsley Hospital.



Of the *surgical clinic cases*\* admitted to hospital with head injury the intervals between the head injury and psychiatric follow-up examination were: two years, 2 cases; three years, 5 cases; four years, 3 cases; five years, 10 cases; six years, 9 cases; seven years, 2 cases; and nine years, 1 case. Thus the majority were followed up five to six years after their accident.

The ages at which head injuries occurred are shown in Table I. Five children had more than one head injury; these are included in each age group where they occurred, giving a total of 35 head injuries in the psychiatric clinic and 33 in the surgical clinic cases. The two groups show a similar age distribution and the peak incidence in both series is in the 5 and 6 year age groups. This peak may be due to the greater exposure to risk of accidents when a child starts school. The causes of the accidents are similar in the two groups (Table I). Road accidents rank highest, accounting for nearly half, while approximately a third result from falls from a height.

Table II compares the severity of the head injuries in both series as judged

TABLE II  
*Nature and Severity of Head Injuries*

|                                       | Psychiatric<br>Clinic Cases | Surgical<br>Clinic Cases | Total |
|---------------------------------------|-----------------------------|--------------------------|-------|
| <b>Fracture Sites:</b>                |                             |                          |       |
| Frontal .. .. .                       | 2                           | 6                        | 8     |
| Fronto-parietal .. .. .               | —                           | 1                        | 1     |
| Parietal .. .. .                      | 3                           | 14                       | 17    |
| Temporo-parietal .. .. .              | 5                           | 3                        | 8     |
| Temporal .. .. .                      | 1                           | 1                        | 2     |
| Parieto-occipital .. .. .             | 2                           | 1                        | 3     |
| Occipital .. .. .                     | 2                           | —                        | 2     |
| Base .. .. .                          | 2                           | 4                        | 6     |
| Vault and vertex .. .. .              | 2                           | 3                        | 5     |
| Total .. .. .                         | 19                          | 33                       | 52    |
| <b>Fracture Complications:</b>        |                             |                          |       |
| Depressed fracture .. .. .            | 3                           | 6                        | 9     |
| Compound fracture .. .. .             | 1                           | 2                        | 3     |
| <b>Duration of Unconsciousness:</b>   |                             |                          |       |
| No fracture but concussed .. .. .     | 16                          | 4                        | 20    |
| Less than 1 hour .. .. .              | 9                           | 11                       | 20    |
| 1-12 hours .. .. .                    | 2                           | 2                        | 4     |
| 12-24 hours .. .. .                   | 4                           | —                        | 4     |
| 1-7 days .. .. .                      | 3                           | 4                        | 7     |
| 7-14 days .. .. .                     | —                           | 1                        | 1     |
| 14-28 days .. .. .                    | —                           | 2                        | 2     |
| Delayed loss of consciousness .. .. . | 1                           | 2                        | 3     |
| None .. .. .                          | 5                           | 4                        | 9     |
| Not known .. .. .                     | 11                          | 7                        | 18    |

by the duration of unconsciousness and the extent of skull fracture. Although these criteria do not necessarily measure the extent of any brain damage, using them as the best available indicators, they show that the surgical clinic cases sustained more severe injuries.

More direct evidence of brain or peripheral nerve injury is given by the number of overt neurological sequelae occurring in both groups. Among the psychiatric clinic cases there was one case of permanent facial palsy and nerve

\* Refers to cases seen at U.C.H., Casualty Ward, or Birmingham Accident Hospital.

deafness, and another with ptosis and nerve deafness. There were two cases of transient hemiplegia and one child developed aphasia and a monoplegia which cleared rapidly. Among the surgical clinic cases there were also 5 children with neurological sequelae. One boy had unilateral blindness and spastic monoplegia. Another had a mild spastic monoplegia which persisted after operation for bilateral subdural haematoma. The other cases were a transient hemiplegia, a right external rectus palsy which cleared after a few weeks and one with temporary facial palsy and permanent unilateral deafness. Although the incidence of permanent neurological sequelae was about equal in the two groups, they were slightly severer in the surgical clinic group.

The period in hospital immediately after the accident can be another indication of the severity of head injury. Except when retention in hospital is due to other factors, such as other bodily injuries, it seems reasonable to infer that cases in hospital for only a few days had less severe head injuries than those retained for a month or more.

Table III shows the periods of hospitalization: the groups do not show marked differences in this respect.

TABLE III  
*Duration of In-patient Treatment Immediately after Head Injury*

|                    |    |    |    |    | Psychiatric<br>Clinic Cases | Surgical<br>Clinic Cases | Total |
|--------------------|----|----|----|----|-----------------------------|--------------------------|-------|
| Less than 1 week   | .. | .. | .. | .. | 3                           | 5                        | 8     |
| 1-2 weeks          | .. | .. | .. | .. | 7                           | 11                       | 18    |
| 2-4 weeks          | .. | .. | .. | .. | 9                           | 6                        | 15    |
| 4-6 weeks          | .. | .. | .. | .. | 5                           | 3                        | 8     |
| 6-12 weeks         | .. | .. | .. | .. | 3                           | 3                        | 6     |
| More than 12 weeks | .. | .. | .. | .. | 2                           | 2                        | 4     |
| Not admitted       | .. | .. | .. | .. | 4                           | 1                        | 5     |
| Total              | .. | .. | .. | .. | 35                          | 33                       | 68    |

#### PSYCHIATRIC ASPECTS

##### *Symptoms*

Table IV shows an analysis of the main symptom groupings. As would be expected the psychiatric clinic cases showed more severe and varied symptoms than the surgical group.

TABLE IV  
*Distribution of Psychiatric Symptoms*

|                                  |    |    |    |    |  | Psychiatric<br>Clinic Cases | Surgical<br>Clinic Cases |
|----------------------------------|----|----|----|----|--|-----------------------------|--------------------------|
| Aggressive behaviour             | .. | .. | .. | .. |  | 19                          | 7                        |
| Hyperactive behaviour            | .. | .. | .. | .. |  | 12                          | 5                        |
| Tics and tension habits          | .. | .. | .. | .. |  | 13                          | 10                       |
| Anxiety symptoms                 | .. | .. | .. | .. |  | 8                           | 6                        |
| Sleep disturbance                | .. | .. | .. | .. |  | 7                           | 3                        |
| Enuresis                         | .. | .. | .. | .. |  | 5                           | 5                        |
| Poor attention and concentration | .. | .. | .. | .. |  | 6                           | 1                        |
| Headaches                        | .. | .. | .. | .. |  | 6                           | 4                        |
| Truancy                          | .. | .. | .. | .. |  | 8                           | —                        |
| Stealing                         | .. | .. | .. | .. |  | 5                           | 2                        |
| Sex delinquency                  | .. | .. | .. | .. |  | 1                           | —                        |
| Fire setting                     | .. | .. | .. | .. |  | 1                           | —                        |
| Asymptomatic                     | .. | .. | .. | .. |  | —                           | 18                       |

Aggressive behaviour with displays of temper and destructiveness was the commonest complaint in the psychiatric group and figured in over half the cases. These children were often described as irritable, quarrelsome, explosive, vicious and spiteful. The comparative infrequency of such symptoms in the surgical group is perhaps the most notable difference between the two groups. It is doubtful if such symptoms are specific for head injury, as some cases were aggressive before the accident and such behaviour is common in emotionally disturbed children without head injury.

Restless, overactive behaviour was complained of in 12 children seen at the psychiatric clinic, but only occurred in 5 cases at the surgical clinic, and in these the symptom was less severe. Symptoms generally accepted as being indicative of cerebral damage in children (hyperkinesis, impulsive behaviour, distractibility and poor attention) were observed in some children of the psychiatric group, but a clear-cut syndrome of this type was absent.

Conduct disorders are grouped under stealing, truancy (including refusal to go to school), sexual delinquency, and fire setting. Such disorders are much more frequent in the psychiatric clinic cases.

Anxiety symptoms, enuresis, tension habits and tics occur with similar frequency in the two groups. Tension habits were mainly nail biting, but included picking and scratching.

Recurrent headaches, often described in the post-concussional syndrome of adults, were noted in only 6 psychiatric clinic cases and 4 of the surgical group. Such headaches sometimes persisted but tended to become less frequent and severe with the passage of time. No case of chronic post-traumatic psychosis or dementia was seen.

### *Pre-traumatic Personality*

Although the cases studied did not fall into clear-cut categories of pre-traumatic personality, an attempt was made to classify them into three groups.

In the psychiatric clinic cases 22 children were rated as normal, or only showing minimal overt psychiatric disturbance before the accident. This group included children who previously showed no psychiatric symptoms and those who showed only minor symptoms in one field of behaviour, e.g. periodic nail-biting or occasional nightmares. After trauma 6 of these cases showed only slight behaviour disorders, 10 cases had moderate or severe disturbances which cleared after a few months and 6 developed prolonged behaviour disorders. In 2 of the last-mentioned cases there was difficulty in assessing the child's personality before the accident. The remaining group of 9 children were rated as having severe emotional disorder before the accident; after trauma, all were major behaviour problems: only one did not remain a long-term problem.

Applying the same criteria to the 32 surgical clinic cases, 31 were rated as normal or only showing minimal overt emotional disturbance before head injury. At follow up after the trauma, 18 were entirely asymptomatic, but 4 of these had suffered from temporary behaviour disturbances for a few months after injury; 9 showed minor disorders of little significance, e.g. nail-biting, etc., 4 showed behaviour problems of moderate severity affecting several aspects of behaviour, e.g. feeding habits, motor habits and sleep. One child was clearly a psychiatric problem before the accident and his behaviour became exaggerated and persisted after it. In the 5 cases with prolonged psychiatric symptoms, 4 had disturbed family backgrounds, which contributed more to the



disorder than the head injury. One boy who showed persistent fear, anxiety and sleep disturbances had a normal family background. In this case the symptoms seemed related to permanent physical handicap in the form of unilateral blindness and spastic hemiplegia.

Though the data were insufficient for precise conclusions, the findings were consistent with the following hypothesis. The prognosis in terms of continued behaviour problems for years after the injury is more directly related to the pre-traumatic emotional state than to the nature and severity of the head injury. Children who show little or no overt disturbance before the trauma may show major behavioural changes for up to a year after the accident, but over a longer period there is a strong tendency to return to normal behaviour. Those children who are serious behaviour problems before an accident show an acute exaggeration of symptoms following head trauma and have a much less favourable prognosis, many showing chronic behaviour disorders. In those cases that exhibit prolonged disturbances after the accident there are very frequently unfavourable factors in the emotional background at home which may have influenced the previous personality. Two examples from the case records may illustrate the prognostic influence of pre-traumatic personality factors.

*J.B.A.*—An 11-year-old boy who was on the waiting list for child guidance treatment when the accident occurred, had spent most of his early life in various residential nurseries. Though shy and solitary at school he was prone to outbursts of temper in the presence of his father and stepmother from whom he frequently sought reassurance that he was loved. Both parents were treated at different times for psychoneurotic symptoms. Before the accident he had been removed from his first school for truancy and later developed asthma, enuresis and encopresis. Following a depressed fracture of the right temporal region he became such an acute behaviour problem that he required urgent admission to a child psychiatric unit. He was aggressive, irritable and explosive, reacting violently to minor frustrations; his asthma was made worse while his encopresis surprisingly ceased. Two years after the accident he was still a serious problem, but showed slightly better emotional control and behaviour.

The second example shows the influence of a good pre-traumatic personality on the prognosis.

*D.W.*—A girl who came from a satisfactory home, showed no evidence of psychiatric abnormality before the accident. Following a depressed fracture of the left parieto-occipital region at the age of 5 she became irritable, restless, aggressive, and cruel to animals. These symptoms, including morbid sexual curiosity, continued for a little over a year, by which time she had nearly returned to her normal state. Follow up eight years after the accident showed her to be asymptomatic and one of the brightest pupils at school.

Of special interest to the previous personality of these children was the tendency to repeated injuries. In the psychiatric clinic series 10 out of 31 children showed evidence of *accident proneness* in that they had a history of two or more major accidents. Using the same definition only 5 out of the 32 surgical cases showed accident proneness. Some cases showed a remarkable predisposition to injury. One boy seen at the psychiatric clinic sustained two head injuries necessitating hospitalization; in the first instance he ran under a lorry and in the second he fell from an upstairs window. In addition to numerous minor injuries he had, although he could not swim, on one occasion plunged into the deep end of the swimming bath and needed artificial respiration to revive him. The same boy had fallen into an open grate, sustaining severe burns. Another boy had, by the age of eleven, on different occasions, fractured his skull, an arm, a leg, he had also injured his eye, and sustained severe scalds from boiling water.

### *The Family Background*

A wide variety of disturbed home backgrounds and faulty attitudes to the child were encountered. In some families these faulty emotional attitudes had clearly contributed to the child's pre-traumatic emotional disturbance. In other cases previously healthy attitudes had changed following the head injury.

Among the psychiatric clinic cases 13 families showed little or no evidence of disturbance in the home atmosphere. In 12 families there was a moderate degree of home disturbance, and in 6 there was severe disturbance of the whole family. The disorders in these families were not specific and included typical broken homes, manifest disturbance in the parental attitude to the child and positive family history of mental disorder. In 8 families there was a history of overt psychiatric disorder in one or both parents.

Among the surgical clinic cases, 22 families showed no evidence of any significant disturbance, though in some of these families there was clear parental over-anxiety about the probable ill effects of the head injury. In 9 of the families there were moderate degrees of disturbance; only 1 was found to be severely disordered. The types of disturbance seen were not distinguishable from those observed in the psychiatric clinic, the difference between the two groups being one of degree. In 5 families one or the other parent had, or was receiving, psychiatric treatment; one mother suffered from paranoid schizophrenia, two mothers had recurrent depressions, another epilepsy, and one father was receiving treatment for anxiety neurosis.

Some severely injured children from normal families made remarkable recoveries, while others with disturbed homes fared badly after much less severe injuries.

The use of the head injury as a scapegoat for later behaviour disturbances was seen in several cases. A clear example not included in this series because the head injury was discovered to be minor, was that of a boy aged 9, referred to the clinic for prolonged and repeated episodes of wandering from home and truanting from school. The mother prefaced her account by saying that at the age of 4 the boy had been involved in a motor accident sustaining a severe head injury with fractured skull, which required ten weeks' treatment in hospital. She added that the surgeon had told her that the boy might experience effects in later life, and that these would take the form of wandering. The data when checked with the hospital concerned revealed marked discrepancies. The boy had been in hospital for a few days, had no skull fracture, and had only been kept in for observation. This boy came from a broken home and he explained during interviews that he hoped to find his father in his wanderings.

## SOMATIC ASPECTS

### *Fracture Site*

The site of the skull fracture is only a remote indicator of the location and extent of the brain injury. Only those cases with depressed fractures, requiring surgical intervention, provided evidence of brain injury at the site of the fracture. Out of 9 depressed fractures, 2 were left frontal, 4 left parietal, 1 left parietal occipital, 1 right temporal and 1 right temporal parietal (Table II). Six of these children made complete recoveries, 1 had scholastic difficulties which could be accounted for by prolonged absences from school as a result of injury and 2 more had major behaviour disturbances. The two cases with

depressed fractures in the frontal region were studied for any evidence of frontal lobe syndrome.

One of them was in the surgical group, a 10-year old boy with normal family background and pre-traumatic personality. Immediately after the accident he required surgical removal of bone fragments. At operation, the dura was intact and after the removal of fragments of bone he was left with a bone defect in the left frontal region of one and a half inches in diameter. He was unconscious for four days and four months later had an operation for plastic closure of the skull defect. Follow-up three years later showed a complete recovery with no behavioural or scholastic disturbances.

The second was a psychiatric clinic case, a boy who at the age of 6 sustained a fracture of the left frontal region. At operation the bone fragments had penetrated the brain and for their removal a left frontal lobectomy had to be performed. Before the injury he had always been difficult to manage, having frequent temper tantrums and breath holding spells. He was aggressive to other children and for two years before the accident he had attended the doctor for treatment of neurotic symptoms (restless sleep with nightmares, morbid fears of animals and threats to leave home). He was a serious problem, and the education authority had recommended child guidance treatment. While awaiting such treatment the accident occurred. The family of this boy was very disturbed: the mother suffered from depression with multiple hypochondriacal complaints, the father was of low intelligence and completely disinterested in the family.

Immediately after the head injury there was a transient exaggeration of symptoms but after a few months the only additional complaint elicited from the boy was that of headache. Two years after the injury he showed moderately disturbed behaviour, and repeated intelligence tests showed I.Q.s around the 90 per cent. level. He was followed up eight years after the accident and when last seen for the purpose of this investigation was making a tenuous adjustment at an ordinary school. He remained very backward, was easily provoked to temper and still had a skull defect which he was apt to palpate anxiously during interview. His disturbed home background remained unchanged.

In neither of these two cases was there any sign which could be attributed to frontal lobe deficit, and in the second case the disturbances had been present before the injury.

### *EEG Results*

Twenty-five patients of the psychiatric clinic group had electroencephalographic (EEG) studies, and in 6 of them serial records were obtained. Six cases had normal records; 3 were borderline or mildly abnormal, and 16 were rated as abnormal. Of the 6 cases with repeated examinations, 4 continued to be abnormal, while 2 showed a diminution of abnormal patterns. Because of practical difficulties only 1 of the surgical clinic cases had an EEG taken because of fits discovered on the follow-up examination. No comparison between EEGs of the psychiatric clinic and the surgical groups is consequently possible.

The EEG was of definite value in the diagnosis and management of those cases having post-traumatic epilepsy. In the few cases in which serial examinations were obtained no clear-cut relationship could be established between EEG abnormalities and behaviour disturbances: some children with normal EEGs showed severe behaviour disturbances, while others, in spite of persistently abnormal EEGs, behaved normally.



Evidence that the behaviour pattern may improve in advance of the EEG was seen in a girl who fractured her skull in the parietal occipital region. After the accident she showed abnormal behaviour and was very difficult to control. EEGs 15 and 16 months after the accident showed marked asymmetry, with a focus of slow waves over the fracture site, but by this time her behaviour had returned to normal.

*Post-traumatic Epilepsy*

In the psychiatric clinic series epilepsy occurred after head injury in 4 cases; 2 were grand mal and 2 had focal or Jacksonian attacks. Among the surgical clinic cases, 2 had post-traumatic epilepsy; 1 was grand mal and the other was a temporal lobe epilepsy.

MANAGEMENT

*Educational Difficulties*

There was a marked contrast between the school problems of the psychiatric clinic cases when compared with the surgical clinic cases. These differences may well be accounted for by selection, as school problems, irrespective of head injury, tend to be referred to child guidance clinics.

In Table V the differences between the 2 groups in educational attainment

TABLE V  
*Educational Attainments Before and After Head Injury*

|                                 | Psychiatric<br>Clinic Cases |             | Surgical<br>Clinic Cases |            |
|---------------------------------|-----------------------------|-------------|--------------------------|------------|
|                                 | Before                      | After       | Before                   | After      |
| Backward .. .. .                | 10                          | 19<br>+4 T. | 2                        | 4<br>+7 T. |
| Average or above .. .. .        | 11                          | 5           | 24                       | 19         |
| Not at school or no information | 10                          | 3           | 6                        | 2          |

T=temporary.

before and after the accident are shown. The psychiatric clinic group contains approximately equal numbers in the backward category when compared with those of average or above ability. In the surgical group almost all the children at school were average or above. If we bear in mind that all children who were backward before the injury remained so after, we can see that an increase in backwardness following head injury is not very different in the two groups. However, in the psychiatric group most of the children show persistent backwardness and slightly greater temporary educational difficulties.

The reason for temporary backwardness was sometimes evident. The child missed a term at school after the accident and was still inattentive and lacking in concentration on his return. Being unable to catch up with his classmates, he became discouraged, often refusing to attempt all but the simplest tasks.

In the surgical group 7 children remained retarded for several terms but subsequently regained average levels. Four children required special educational treatment, 2 at schools for physically handicapped pupils, 1 at an open-air school, and the other had developed sugar diabetes a year after head injury and had been sent to a residential school for diabetics.

Of the 11 children in the psychiatric clinic group requiring special educational treatment, 7 were placed in schools for educationally subnormal

pupils; 2 in schools for physically handicapped pupils and 2 in schools for maladjusted pupils. A further 4 were thought to be in need of special educational treatment but this was not carried out for administrative reasons connected with the education authority.

Comparison of the school placements show that the special educational category was determined in all 4 of the surgical group by physical incapacity, while in the psychiatric group only in 2 out of 11 was this so.

Teachers' attitudes were found to be important. One boy had a small skull defect, not requiring plastic closure, and had been forbidden all games and most recreational activity by the headmaster. This opinion had been backed by the school doctor and it required a firm letter from the surgeon indicating the very remote risks involved before the boy was allowed to lead a normal school life. In many other cases the need for a close liaison between the school and the clinic was obvious.

One child with a mild hemiplegia and post-traumatic epilepsy following a head injury in the second year of life, entered a school for physically handicapped children at the age of 4½ where she was stated to be happy and making good progress, though she remained backward for her age. Behavioural difficulties began when a transfer of school was caused by a change of abode. In the new school she made no progress, was unhappy and reluctant to go to school. A visit to the school paid independently by a psychologist and later by a social worker revealed difficulties; the classes were overcrowded, the head mistress was impatient with children showing behaviour difficulties and the form mistress was not interested in backward children. The child was regarded as the school failure. In this case it was not difficult to see that little progress could be made in treatment until a more suitable school had been found.

Full psychological testing was of great value in the management of these educational problems. All the psychiatric clinic cases were subjected to routine assessment of intelligence: the tests used for this purpose were the Stanford Binet and the Wechsler Intelligence scale for children. In only one instance was testing carried out before the head injury. Test results showed that 12 children had I.Q.s between 100–120, 13 between 80–100, 4 between 60–80 and the remaining 2 were below 60. Only 5 of the surgical cases were selected for psychological testing, though each child was clinically examined for general knowledge and intelligence. Those who were tested were given the Kent Oral Emergency Test and none of them scored below average in intelligence. It was felt that none of the remaining children examined clinically were of subnormal level.

Those children in the psychiatric clinic group who had school problems were assessed for their educational attainments on the Schonell tests in reading and arithmetic. Thirteen cases were found to have a discrepancy between their I.Q. and the expected educational levels in reading, arithmetic or both. It was clear that in many cases educational backwardness was present before the accident and could not be attributed to it. These tests did however indicate those children who required remedial education, which was then carried out by the staff psychologist or through the education authority.

An example of the value of psychological investigation was seen in a boy who at the age of 5 sustained multiple skull fractures, which were followed by transient speech difficulties. When examined 14 months after the injury he had an I.Q. of 91 on the Binet and a full scale I.Q. on the W.I.S.C. of 91 (verbal 104, performance 90). Testing on Porteus Maze and Strauss Marble Board were typical for brain injured groups. Variation in subtest scores suggested intellectual impairment. Educational tests showed marked retardation. He was

poor in tests demanding attention, concentration and persistence and the results showed low scores for immediate memory. He was taken on for individual coaching by a psychologist, who found he would only attend for short periods of time and reacted strongly to failure, becoming easily discouraged. During the coaching sessions he was distracted by minor details. It was found that he could learn best by the use of a tracing technique and coloured letters. The results of the tests were useful also in pointing out to the education authority that he was not defective but had learning handicaps which could not be dealt with in an ordinary school, in spite of his average I.Q. He had continuous coaching for 18 months, but though improved, remained three years retarded in every subject. When last examined he had been at a special school for 3 years and had shown a gradual all round improvement except in his reading, with which he still had serious difficulties.

The only other case in which it could be assumed with confidence that considerable intellectual impairment had taken place was a boy who sustained a depressed fracture of the temporo-parietal region of the non-dominant hemisphere at the age of 11. His performance at school before the injury indicated good average ability in class, and he had just passed the entrance examination to a central school. From this it was inferred that his I.Q. before the accident was unlikely to have been less than 100. Repeated testing between six and eighteen months after his injury showed consistently dull or borderline levels of intelligence with I.Q.s on different tests ranging from 75 to 86. Further testing indicated that ability to abstract and to shift his attention was low. None of the test results were consistent with his previous average ability. Recent follow-up indicated some improvement in school performance.

While full psychological testing is important, it is dangerous to predict the long-term effects on intellectual function in head injured children on the basis of test results alone. A boy, who at the age of 14 sustained a fractured base of the skull, was tested on the Wechsler, Shipley Hartford and Alexander Performance Scale and the results reported as consistent with severe intellectual deterioration. Follow-up six years later showed that the patient held a stable position as a draughtsman and was well adjusted.

It is always difficult to assess to what extent the head injury is the cause of intellectual defect. Only in one case in our series was there objective evidence on the level of intelligence before and after the injury. A boy aged 4 years was admitted to hospital for investigation and found on testing to be severely defective (I.Q. below 50). While awaiting admission to a colony for defective children he sustained a head injury. He was semi-comatose for two days and had left-sided Jacksonian fits, X-ray of the skull showed an occipital fracture. Following the acute phase he recovered fully; his behaviour and test results showed the same level of defect as before the injury.

With the exception of the cases of post-traumatic epilepsy, where anti-convulsants were given, no drugs were used routinely to control symptoms.

Each individual case in the psychiatric clinic group was assessed and treated in the same way as other children in the clinic presenting behaviour problems without head injury. In fact, special care was taken not to emphasize the head injury in treating the child.

#### DISCUSSION

The series reported here highlights the major importance of other factors apart from the head injury in assessing the outcome of post-traumatic psychiatric disorders in children.



It would be expected on grounds of selection that children seen in a psychiatric clinic and found to have a history of head injury would differ from children whose criteria for selection was previous admission to a children's surgical ward with head injury. Analysis of the results shows that, using the presence and extent of fracture, the duration of unconsciousness and severity of neurological sequelae as criteria of severity, the children followed up from surgical cases had more severe head injuries. Assuming that head injuries were the only major factor producing subsequent psychiatric disorder, one would expect that the surgical clinic cases would have shown at least as much, if not more, behaviour disorders than the psychiatric clinic cases. Apart from anxiety symptoms and minor tension habits this was not found. It would seem justifiable to infer therefore that many of the chronic symptoms seen were not attributable to the head injuries alone, but were products of other factors, such as the family background, pre-traumatic personality and intelligence, and might well have manifested themselves in many cases without head injury.

Apart from anxiety symptoms and other more trivial disturbances the surgical clinic cases who presented psychiatric problems of note invariably had adverse environmental factors which could adequately explain the behaviour without postulating a traumatic aetiology. The common parental allegation that "it all started when he hit his head" must be accepted with reserve in that two children with comparable injuries may have entirely different psychiatric prognosis.

Some authors have stressed the importance of a special organic syndrome in children following head injury, e.g. Bowman and Blau (1943), Lutz (1951). In this syndrome, symptoms such as memory disturbances, affective changes and disturbed impulses are described. Another organic syndrome seen after encephalitis and consisting mainly of a severe conduct disorder, has also been described after head injury by Ebaugh and Strecker (1924), Kasanin (1929), and Lutz (1951). In our material individual symptoms of the type described in both these syndromes were sometimes seen, but the specific grouping of symptoms described by these authors was absent in both series. In our view the symptoms described in these syndromes are not distinguishable from those frequently found in children suffering from neurotic behaviour disorders.

The influence of the pre-traumatic personality on the result of head injuries in adults has been stressed by many authors, notably by Symonds (1937), who epitomized the matter by indicating that it is not only the kind of head injury that matters but the kind of head; and also Lewis (1942) who expressed the view that a post-head injury syndrome is apt to occur in much the same person who develops a psychiatric syndrome in other circumstances without any head injury at all.

The influence of the pre-traumatic personality in children has attracted less attention. Crothers and Lord (1938) made a careful study of two cases of severe head injury in children, and provided information about their pre-traumatic personality. In one case there was an exaggeration of previous personality trends. The other child had a normal pre-traumatic personality and remained well adjusted in spite of severe prolonged neurological sequelae. Riggenbach (1946) reported that in cases of long-lasting sequelae this was due in the majority of cases to an abnormal pre-traumatic personality or physical handicap and only very rarely to an extremely severe trauma. Fabian and Bender (1947) found predisposing conditions in about one-fourth of 86 children who manifested behaviour disorder associated with head injury. These predisposing conditions included mental retardation, epilepsy preceding brain

damage and psychosis. In this series the presence of pre-traumatic emotional disturbance with behaviour disorder and educational backwardness was very common in children whose course showed a persistent major psychiatric problem after the accident.

These findings bring the psychiatric sequelae of childhood head injury more into line with the assessments of post-concussional and post-contusional states in adults.

The literature on accident proneness in children is limited, but studies by Ackerman and Chidester (1936), Fabian and Bender (1947), Fuller (1948), Langford and her associates (1953) have indicated the importance of various factors where there is a tendency to repeated accidents. The incidence in the psychiatric clinic cases was double that observed in the surgical clinic and confirms the underlying importance of psychological factors in proneness to head injury.

The possibility that the site of the fracture might have some influence on the subsequent psychiatric disturbance has attracted the attention of a number of authors, notably Blau (1936), who felt that the occurrence of a fracture in the frontal region in 5 out of 9 post-traumatic behaviour disorders suggested that these disorders may result from a localized lesion of the prefrontal association areas of the brain. There is little evidence from this series that, apart from specifically demonstrable neurological defects, the fracture site has any special significance for after effects.

Fabian and Bender (1947) found that the majority of 86 children who manifested behaviour disorders associated with head injuries came from highly disturbed home environments with parents suffering from alcoholism or psychiatric disorders. A notable feature in the investigation of the family background in this series was the high incidence of psychiatric symptoms in one or other parent, together with emotional disturbance in the home, particularly in those cases who continued to show prolonged behaviour disorders. The disturbed family background affected not only the pre-traumatic personality but also maintained abnormal conditions which hindered recovery. Kanner (1950) stressed head injury as a scapegoat to explain behaviour disorders in children which were in fact related to other causes. Many parents of children examined in this series had the idea that injuries to the head must inevitably have more serious consequences for the child's future than accidents to other parts of the body. This emotional loading accorded to the head in our culture creates a pessimistic expectation and fear among parents, which needs correction in light of the generally favourable outlook in the absence of predisposing factors.

The management of the chronic post-traumatic behaviour disorders presents a difficult problem. Ssouchareva and Einhorn (1935) noted improvement in capacity for work and emotional adjustment after admission to a psychiatric centre with the tendency to relapse on discharge, and they advocated close collaboration between doctors and teachers with special emphasis on remedial education, and in some severe cases, psychiatric institutions. Bowman and Blau (1943) also found the usual methods of training and discipline in reform schools were unsatisfactory and that special facilities in state mental hospitals were required. This survey shows the need for full out-patient and in-patient child psychiatric services for the few of these cases, and in particular the need for special educational provisions for these disturbed children, who should, if possible, be treated in an educational setting rather than in a mental hospital or institution. The importance of backwardness and educational

retardation as revealed by psychological tests was notable, and points to the real need of a co-operative effort between the psychiatric clinic and educational authorities in treatment.

#### SUMMARY

This study was undertaken to investigate the long-term psychiatric sequelae of head injuries in children. Thirty-one head injured children attending a child psychiatric clinic were compared with 32 children of similar age who had been admitted with head injuries to a surgical ward some years previously. The children from surgical sources had sustained more severe head injuries as judged by the presence of skull fracture, duration of unconsciousness, and neurological sequelae, but, as had been predicted, they showed far less psychiatric disorder than those examined at the child psychiatric clinic. A wide variety of symptoms were encountered but few appeared to be specific or causally related to the head injuries. The fracture site had no clear relationship to subsequent behaviour disorder. The pre-traumatic personality and family setting were far more important for the psychiatric outcome than the nature and severity of the head injury. A generally favourable outcome even after severe head injury in previously well-adjusted children was confirmed, but where children showed evidence of marked emotional disturbance before the accident, the outcome was far less favourable and dependent on the persistence of adverse factors at home. The families of children who showed chronic post-traumatic disorders showed a high incidence of psychiatric disturbances. Accident proneness was twice as frequent in the psychiatric clinic cases, and there was evidence that this was related to emotional disorder. In the management of the psychiatrically disturbed cases the educational aspects were found to be of primary importance and in these cases full psychological investigation and special remedial teaching was an important aspect of treatment.

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# A CONTROLLED INVESTIGATION OF THE EFFECTS OF CYCLIZINE HYDROCHLORIDE IN CHRONIC PSYCHOSIS

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## INTRODUCTION

CYCLIZINE hydrochloride (1-benzhydryl-4-methylpiperazine monohydrochloride) is a popular remedy for motion-sickness. The success which is reputed to attend the use of the drug in this condition may be a function of of two distinct effects: (a) a direct, specific inhibition of the vestibular mechanism; (b) a general, central inhibition or sedation. A consideration of the latter, rather than the former, suggested the possibility that cyclizine might prove to be of value as a potential "tranquillizer". A controlled clinical trial was carried out in order to establish whether any tranquillizing effects might be associated with the use of the drug in a number of chronic psychotics, all of whom manifested some gross disturbance of behaviour. This paper describes the experimental method which was used; the results which were obtained; and a general comment upon the possible implications of the results in relation to other drugs used in psychiatry.

## METHOD

The object of the trial was to establish whether cyclizine is a potential tranquillizer. A necessary preliminary requirement to the resolution of this problem was to have a satisfactory set of criteria by which the tranquillizing properties of the drug were to be judged. It was necessary, therefore, for the purposes of our investigation that we should select, albeit somewhat arbitrarily, certain criteria by which a fair and reasonable judgment might be made as to the tranquillizing properties of cyclizine. To resolve this difficulty the hypothesis was postulated that if cyclizine is a tranquillizer then it might be expected to modify favourably the behaviour, and perhaps the total clinical picture, of certain patients who objectively may be seen to be in a state very far removed from what might be described as tranquil. The patients we selected to test this hypothesis were chronic deteriorated schizophrenic psychotics, all of whom clearly displayed some visible form of abnormal behaviour or activity. The most disturbed male ward in the hospital was chosen as that portion of the patient population most likely to furnish the required patient material. From a total of 90 patients in this ward, 30 patients were finally selected for inclusion in the trial. They were considered, by the nursing and medical staff alike, to

be the most disturbed patients in the ward, all of whom were known to be restless, noisy, or aggressive.

The next requirement was to decide upon suitable standards by which, during the course of the trial, a change, for better or worse, in the behaviour and clinical state of the individual patient might be validly recorded. This, in turn, entailed the need for the selection of a variety of observations to be made during the trial which would incorporate the required standards for determining change in the patients, and, in consequence, test the tranquillizing properties of cyclizine. Three basic types of observation were selected as those which, in conjunction, would prove most likely to provide an objective and comprehensive judgment or standard of change in the trial patients. These three different types of observations were to comprise: (a) the numerical scoring upon a 4 point—23 item psychiatric rating scale; (b) the recording of global or conventional clinical judgments; (c) the registration of abnormal incidents on behaviour charts.

(a) The rating scale was specially designed for the trial, and covered a wide range of symptomatic abnormalities relating to the function of intellect, emotion, and behaviour. The scale was so constituted that a high total score, recorded for a particular patient, would represent gross abnormality; and, conversely, a low score would indicate relatively slight deviation from the so-called "normal". A reduction in the initial score of a patient on the scale, during the course of treatment, would be taken to imply a therapeutic gain; an increase in the initial score representing a deterioration. For convenience, and for the purposes of the final analysis of the results, the difference between a patient's initial and subsequent score was to be designated his "improvement" score. A reduction in his initial score would provide a positive "improvement" score; an increase would yield a negative "improvement" score.

The initial and subsequent ratings were to be carried out by the two investigators (F. and C.); each of whom would act as his own control by retaining the same 15 patients, allocated to him at random, for rating purposes throughout the trial. However, in order to test the validity of the scale to some extent in advance, and to see if a consistency obtained in the ratings of the two investigators, 10 patients, other than those included in the trial but similar in symptomatology, were independently rated by both F. and C. The correlation coefficients, which were found to obtain between the two raters, were of a high order of significance.

- (i) Product-moment,  $r=0.85$ , with df. 8,  $P=<0.01$ . Significant at the 1 per cent. level of confidence.
- (ii) Rank difference,  $\rho=0.89$ . Standard error  $=0.33$ . Significant at the 1 per cent. level of confidence.

("Significance" at the 1 per cent. level, in this context, indicates that a consistency as great as that observed to obtain between the two raters, would be expected to occur only once in a hundred repetitions of the ratings, upon the basis of pure chance alone. The conclusion which may be drawn from the  $P$  values obtained, and their 1 per cent. confidence levels, is that the two raters obtained a high degree of consistency in their ratings and that, therefore, there is some presumptive evidence that the rating scale itself was really measuring with some degree of reliability.)

(b) The global or conventional clinical judgments, which were recorded throughout the trial, were made by the two investigators, upon the same 15 patients assigned to each for rating purposes. These judgments were made without

the previous rating scale scores, or assessments, being available at the time to the investigator, in the interests of the independence and objectivity of the various observations being made. The global assessments were to be based upon 5 discrete categories of overall clinical response, namely: Great improvement; Moderate improvement; Slight improvement; No change; Worse.

(c) The behaviour charts were to form a daily record, kept by the nursing staff, of all the noisy outbursts, aggressive acts, and incidents of incontinence and insomnia of each of the patients during the trial.

Certain controls were used to render the recording and interpretation of the observations as valid and objective as possible. A placebo (calcium lactate) was used in conjunction with cyclizine, so that direct comparisons might be made between the effects of the latter and those of what is generally accepted to be a pharmacologically inert substance. "Group" control was used during the first two weeks of the trial; 15 patients having been assigned at random to a cyclizine treatment group, and 15 patients to a placebo group. "Self" control was substituted for the former "group" control during the second two weeks of the trial, when each patient was changed over to the opposite treatment or preparation to that which he had been receiving during the first two weeks. By this method the response of a cyclizine group might be compared with that of a placebo group for the first two weeks of the trial. Furthermore direct comparisons might be made between the individual responses to each of the preparations, cyclizine and placebo, for all 30 patients included in the trial.

The tablets of cyclizine and placebo were identical in appearance, and were to be administered to the patients on a "blind" basis throughout the trial. The random assignment of patients to the two "treatment" groups, cyclizine and placebo, for the first 2 weeks of the trial, was effected in the following manner: The dispenser was given a code which consisted simply of the numbers 1-30 allocated at random to two groups A (cyclizine) and B (placebo), each group being represented by 15 numbers. The names of the 30 trial patients were sent to the hospital records clerk, with the request that he arbitrarily pair with each name a number between 1 and 30 inclusive, using each number once only. He was further requested to dispatch the paired names and numbers to the dispenser in a sealed envelope. In this way the preparation which a particular patient received during the first two weeks of the trial was determined by whether the number paired with his name, by the clerk, corresponded with Group A or Group B of the dispenser's Code. For the second two weeks of the trial each patient received the opposite preparation to that which he had already received during the first two weeks.

This system ensured, from the outset, that the cyclizine and placebo groups would be equally represented by 15 patients each; that the two groups would be unselected or unbiased in terms of the total test sample of 30 patients; that the composition of the 2 groups would be unknown to the investigators until the final decoding at the end of the trial; that each patient would receive consecutively the two preparations, cyclizine and placebo, or vice versa; and that the dispenser alone would know, at any time during the trial, which of the two preparations any particular patient was receiving.

In order that any observed changes or therapeutic effects might reasonably be ascribed to the two preparations, no other form of treatment, physical or medicinal, was administered to the patients during the trial; and the environment was stabilized in so far as that was possible.

The statistical techniques, by which any valid judgments might be made



concerning the "significance" of any observed differences in treatment effects between cyclizine and placebo, were decided upon in advance and with reference to the basic observations for recording change in the patients, which have already been described. The techniques were to be of two types, namely, a "t" test to be applied to the rating scale scores; and a simple Chi-square test to be applied, independently, to the global assessments and behaviour incidents.

The intention was to obtain an initial "score" on the rating scale for each patient at the commencement of the trial, and a subsequent score at the end of two weeks. From these scores the individual "improvement" scores for each patient were to be determined. The Mean Improvement Scores for the cyclizine and placebo groups might then readily be calculated; and the "significance" of any difference between these two means might be computed by a "t" test. If the mean initial scores for the cyclizine and placebo groups showed a marked disparity, one assumes that it would have been necessary to carry out a covariance analysis to "adjust" for this discrepancy. However, as can be seen in Table I, the mean initial scores for the two groups proved to be identical,

TABLE I  
*Rating Scale Scores for First Two Weeks of Trial Using Group Control*

| Placebo Group<br>(15 patients) |                  |                |                           | Cyclizine Group<br>(15 patients) |                  |                |                           |
|--------------------------------|------------------|----------------|---------------------------|----------------------------------|------------------|----------------|---------------------------|
|                                | Initial<br>Score | Final<br>Score | Improve-<br>ment<br>Score |                                  | Initial<br>Score | Final<br>Score | Improve-<br>ment<br>Score |
| Total ..                       | 464              | 428            | 36                        | Total ..                         | 464              | 444            | 20                        |
| Mean ..                        | 30.9             | 28.5           | 2.4                       | Mean ..                          | 30.9             | 29.6           | 1.3                       |

$t=0.48$ , df. 28,  $P>.05$ ; (t value of 2.05 required for significance at 5 per cent. level of confidence).

30.9 for both. (A testimony to the capacity for randomization to achieve a remarkable degree of parity.) As a result of this, no such "adjustment" was necessary to the initial scores, and a "t" test could validly be applied to test the significance of any difference in the subsequent Mean Improvement Scores for the two groups. With regard to such factors as diagnostic types, severity of illness, age, and duration of illness, etc., the two groups were equally comparable. For example, all the patients were males, and all were chronic disturbed schizophrenics; the average duration of illness was found to be identical for the two groups, being 21.3 and 21.3 years.

Global or clinical assessments were to be made on each patient at the end of 2 weeks, and again at the end of 4 weeks, by which time all 30 patients would have received both preparations. A total of 60 such assessments would then be available for analysis with 30 of them coinciding with the administration of cyclizine, and 30 with placebo. These two sets of 30 clinical assessments might then be directly compared, and the "significance" of any difference between them determined by a Chi-square test. (In the final event 2 sets of 29 such assessments were available for comparison, as one patient was withdrawn from the trial after two weeks, as a result of anorexia.) The totals of abnormal behaviour incidents as abstracted from the appropriate charts, and identified as having been associated with cyclizine or placebo treatment respectively, were to be subjected, like the global judgments, to a Chi-square test of significance.

The trial was to be of 4 weeks duration. Each patient was to receive, either in the first or second 2-week period of the trial, 150 mg. of cyclizine

daily by mouth, followed by 300 mg. daily for a further week, in the form of tabs. 50 mg. 1 t.d.s. and tabs. 50 mg. 2 t.d.s., respectively. Likewise, each patient was to receive placebo as tabs. 1 t.d.s. for one week, followed by tabs. 2 t.d.s. for a further week; either in the first or second period of the trial. The method by which it was determined as to which of these two regimens a particular patient received first, or second, has already been described.

No specific attempt was made to investigate the toxicology or side-effects of cyclizine during this trial. The compound has been on the market long enough now for it to be considered comparatively safe and non-toxic; and moreover any conclusions concerning its toxicity based upon such a short trial as this, would be both presumptuous and insignificant against the background of what is already known about the compound in this respect.

### RESULTS

The results of all the observations made during the course of the trial are presented in summary form in Tables I to III. Underneath each Table the result

TABLE II

*Global Assessments for Whole Trial, with Each Patient Acting as His Own Control*

| Response    |    |    |    | Cyclizine<br>Periods | Placebo<br>Periods | Total |
|-------------|----|----|----|----------------------|--------------------|-------|
| Improvement | .. | .. | .. | 8                    | 12                 | 20    |
| No change   | .. | .. | .. | 19                   | 14                 | 33    |
| Worse       | .. | .. | .. | 2                    | 3                  | 5     |
| Total       | .. | .. | .. | 29                   | 29                 | 58    |

Combining categories "worse" and "no change":  $\chi^2=0.68$ ,  $df=1$ ,  $P=.4$ ; (Chi square value of 3.84 required for significance at 5 per cent. level of confidence).

TABLE III

*Abnormal Behaviour Incidents Recorded During Trial*

|             |    |    | Noisy<br>Outbursts | Aggressive<br>Acts | Incontinence | Insomnia |
|-------------|----|----|--------------------|--------------------|--------------|----------|
| Cyclizine   | .. | .. | 143                | 5                  | 21           | 11       |
| Placebo     | .. | .. | 134                | 9                  | 28           | 11       |
| Total       | .. | .. | 277                | 14                 | 49           | 22       |
| Differences | .. | .. | $P>.05$            | $P>.05$            | $P>.05$      | —        |

of the appropriate statistical analysis is stated in the conventional manner. The analyses are, in each instance, based upon the null hypothesis which is a necessary and fundamental pre-requisite. In the present analyses the null hypothesis states that "there is no difference in the treatment effects between cyclizine and placebo and any observed differences, therefore, are attributable to chance". The P values then indicate in what percentage of a number of repetitions of the trial, differences as large as those observed to obtain between cyclizine and placebo, would be expected to occur on the basis of "chance". A P value of .05, or less, indicating that such differences would be expected to occur by chance in only 5, or less than 5, out of a total of 100 repetitions of the experiment, is generally accepted by convention as justifiable grounds for rejecting the null hypothesis. Rejection at the 5 per cent. level of confidence, as it is termed, would imply that the observed differences between cyclizine

and placebo probably reflected real differences in treatment effects. It would not, and indeed by its very nature could not, rule out absolutely, however highly significant the P value, the possibility that chance was the operative factor. None of the P values, as may be seen recorded, reached anything approaching the 5 per cent. level of confidence, and so there are insufficient statistical grounds for rejecting the null hypothesis. The conclusion necessarily follows that the trial results failed to differentiate between the treatment effects of cyclizine and placebo.

### DISCUSSION

In reflecting upon the trial as a whole certain salient points emerge. Their importance may warrant individual consideration in some detail.

The "blindness" of the trial which is of such paramount relevance to the objective validity of the results, was effectively preserved throughout. A variety of factors may have contributed to the success of this aspect of the investigation, including some, if not all, of the following: (i) Scrupulous randomization coupled with a fixed and pre-determined design which is inexorably adhered to throughout; (ii) A deliberate restriction of the object of the trial to an exploration of the therapeutic, as opposed to any toxic, effects of the drug; (iii) The singular freedom of cyclizine from any obtrusive and identifiable side-effects; (iv) An objective and scientific orientation to the trial as an experiment, rather than any disproportionate interest or pre-occupation with the test preparations themselves; (v) The comparatively short duration of the trial; for given enough time, however slight the side-effects of the test compound, "the penny will drop" and it is for this reason that the "blindness" must be suspect of those trials in which a particular preparation is administered to the same patients for a period extending over many months.

The three main, and different, types of observations, recorded in the course of the trial, contributed consistently to the same answer; namely, that cyclizine was not more therapeutically efficacious than the placebo. Such an observed consistency, between different data, provides a more reliable and convincing answer than deductions based upon one set of clinical observations. Objective and verifiable facts, such as behaviour incidents, provide a valuable check on the more subjective impressions of the clinician. The greater the number and variety of relevant clinical observations, recorded during a trial, the more reliable and comprehensive may be the final assessment of the test drug.

The imperative need for placebo control, when attempting to assess a new drug, has been pre-eminently illustrated. Cyclizine was associated with a 28 per cent. recorded improvement rate, in terms of conventional clinical judgments. This might all too readily have given rise to excessive enthusiasm, and false specific claims, were it not that the 41 per cent. improvement rate associated with the placebo afforded a proper perspective for viewing the therapeutic performance of cyclizine.

The recorded clinical observations must be subjected to some form of statistical analysis before any reliable deductions can be made from them. Simply "looking at" the two improvement rates of 27.6 per cent. and 41.4 per cent. for cyclizine and placebo respectively, might give one the impression that there is a noteworthy or significant difference between them. The application of a simple statistical test to the difference between these two proportions may help to dispel such an illusion. (Difference in proportions=13.8, Standard Error=12.35, Difference not statistically significant.) It is frequently and derisively suggested that "statistics can be made to prove anything". This,



however, is a travesty of the truth. Statistics can never provide proof of a cause and effect relationship, and no reasonable statistician, one imagines, would ever claim that they could. They may, nevertheless, enable one to formulate a precise statement as to how often the observed results of an experiment might be expected to occur again upon the basis of chance alone in a specified number of repetitions of that experiment. In fulfilling this function of determining the "probability" of observed phenomena, statistical method and analysis become the arch-enemy of wishful thinking.

The compelling need would seem to be for stringent and disciplined comparative trials of all new tranquillizers before any unsubstantiated claims, however eloquent, should be accepted. The necessary scientific discipline is exemplified by the work of Hargreaves *et al.* (1), Raymond *et al.* (2), Thorpe and Baker (3), from which we personally have derived much of our methodology, and we would like to acknowledge our debt to these authors in particular. The new biochemical approach to psychiatry, which is so full of rich potentialities, may benefit if unbridled enthusiasm is checked by the rein of critical enquiry.

#### SUMMARY

A "blind" controlled trial of cyclizine in the short-term treatment of chronic psychosis was carried out. The object was to determine whether cyclizine is a potential tranquillizer. Thirty chronic disturbed schizophrenics received cyclizine and a placebo alternately. The design enabled group comparisons to be made between the effects of the two preparations, and also afforded direct comparisons between the responses of each individual patient to both preparations administered consecutively. The criteria of therapeutic response were based upon rating scale scores, clinical assessments, and the recording of abnormal behaviour incidents. A simple statistical analysis failed to reveal a "significant" difference between the treatment effects of cyclizine and placebo in terms of the observations made on the 30 patients included in the trial. From this it was deduced that cyclizine is not a specific tranquillizer. However, a considerable improvement rate was recorded for both preparations, and the possible implications of this fact were emphasized in relation to the extravagant claims so frequently made for tranquillizers in general.

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# EFFECTS OF LSD-25 ON TESTS OF PERSONALITY

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## INTRODUCTION

THE present analysis pertains to the experiment reported by Brengelmann, Pare and Sandler (15) to assess the effect of 5-hydroxytryptophan (5-HTP) on lysergic acid diethylamide (LSD) by means of psychological tests. In the following, problems of measurement and validity of the LSD- "psychosis" are discussed.

The psychopharmacology of LSD has recently been reviewed by Rubin (20,) who closes his section on psychological effects by stating that "the pattern of impairment has not as yet been compared to that which may characterize the functional psychoses". This is the main aim of the present analysis.

Referring to Rubin's review, results to date show that as a result of LSD administration test responses may vary, or may not vary, in the direction of psychotic-like responses. In contrast to this, no results appear to have directly contradicted the hypothesis that LSD acts to increase psychotic-like effects. Where results did not vary in the expected direction they simply remained insignificant. In these cases (compare 1, 2, 17, 18) it may be argued that the tests used were not of a sufficient degree of difficulty or that the amount of LSD given was too small. The severity of a testing of the hypothesis that LSD produces psychotic-like symptoms might then be increased by two means: firstly, by varying the conditions of test administration so as to produce more specific effects and, secondly, by including tests of a greater variety known to discriminate significantly between psychotics, on the one hand, and normals—or other abnormals—on the other.

The former step was taken by the present author in a previous publication (14). Following injection of LSD, a memory recall impairment specific to relatively long, as against short exposure time, was obtained. The specificity of this effect was subsequently tested on clinical groups of schizophrenics and neurotics (12). The hypothesis that schizophrenics perform worse than neurotics specifically after long exposure (30 seconds), as against short exposure time (2 seconds), was confirmed in both the male and female subgroups used.

In the present experiment the second of the two methods, referred to above, was chosen. The hypothesis was tested that LSD-treated normals react in the same way as psychotics, or schizophrenics, in a series of tests previously validated against psychosis. Confirmation of the hypothesis would tend to strengthen the assumption that LSD produces in normals a psychotic reaction, that is, one in which all the measurable characteristics are also found in the clinical psychoses, particularly schizophrenia.

## METHOD

### *1. Subjects and Drug Administration*

Normal volunteers with an age range of 25 to 31 years were given 60  $\mu$ g of LSD in 10 ml. water intravenously. Injections took place on two occasions,

preceded either by 25 mg. of DL-5HTP in 5 ml. solution or an equivalent volume of placebo. The latter two injections, administered on subsequent days, were randomized using a balanced design so as to avoid sequence effects. Neither the subjects nor the psychologist knew, until he had scored the results, whether 5HTP or placebo had been given.

## 2. Test Administration

The tests were given one day before the first injection in order to control for practice and to familiarize subjects with the situation. Randomizing order A and B of tests and injections over the subjects taking part, the following basic schedule was employed. Testing started 30 minutes after each injection and was completed within the next hour.

|   |    |    | <i>First Day</i> | <i>Second Day</i> | <i>Third Day</i> |
|---|----|----|------------------|-------------------|------------------|
| A | .. | .. | Practice         | 5HTP-LSD          | Placebo-LSD      |
| B | .. | .. | Practice         | Placebo-LSD       | 5HTP-LSD         |

From this it may be seen that the placebo-LSD comparison, exclusive of 5HTP-LSD, is logically objectionable. In the case of schedule A, more practice precedes the placebo-LSD conditions than in schedule B. Additionally, the order of LSD following placebo is constant. Although it is granted that these differences in amount of practice may affect the analysis to a certain degree, they will have no qualitative effect for empirical reasons. Firstly, the data reported show conclusively that the trends in test score variation are practically exclusively due to LSD and not to differences in testing occasions (days). Secondly, as may be seen from the associated publication already quoted (15) LSD produces essentially the same results when following 5HTP, as compared with placebo, though to a lesser extent.

## 3. Description of Tests

Tests and scores used in the present experiment are described as follows:

(a) *J-A-H Rating Scale*. Jarvik, Abramson and Hirsch (19) developed a 59-item rating scale containing physiological, perceptual and cognitive questions to assess changes due to a variety of drugs. Under the conditions used by these authors, response deviation from placebo condition was largest for LSD. In the present experiment 5-point ratings, ranging from 0 to 4 were used.

The score was the sum of ratings over all 59 questions (range 0 to 236).

(b) *Perceptual Reaction Test (PRT)*. This test, devised by Berg (4), consists of 60 abstract designs. The subject was asked to rate each design by choosing one of the following grades: like much (+2), like slightly (+1), neutral (0), dislike slightly (-1), or dislike much (-2). Barnes (3) has shown that psychotics, in particular schizophrenics, scored high on extreme "response set", or "Einstellung". This result was mainly achieved via the *positive* extremes (+2). The present author has obtained the same results using two widely differing techniques, an item check list to assess how much a subject wants a personal friend to possess certain characteristics (12), and a recognition test described below (FRT recognition). These three pieces of research have a common denominator in that the "positiveness" of response is a conspicuous feature of schizophrenic behaviour.



The score used was: *mean degree of likes*, multiplied by 100 (range -200 to +200). Extreme responses (+2 and -2) were analysed separately, but yielded no essentially different results.

From other tests, probably falling in the same category as those already discussed in the present section, it is known that variability of response in judging photographs (16) or in colour choice (8) is higher for psychotics than for both normals and neurotics. For this reason, a PRT-Variability score was derived by computing the degree of response change between practice trial and any of the four following drug trials. If, during practice, an abstract pattern of the PRT had been "liked much" (+2), but "disliked slightly" (-1), say, after the injection of LSD, a response change of 3 was scored (similarly: from +2 to +1=1, from 0 to -2=2, etc.). Scores were summed over the 60 designs. In order to control for practice, response change was additionally scored separately for testing days, i.e. change from "placebo" to "LSD" and from "5HTP" to "LSD".

The main score used was: *degree of variability*, or response change, from practice trial to any of the four drug trials; additionally: change between placebo-LSD and 5HTP-LSD.

(c) *After-image Duration*. The test used has been described previously (5, 7). The stimulus, a red square of 5 cm.  $\times$  5 cm. mounted on a grey background, was exposed in dim light for 20 seconds. Viewing distance was 50 cm. and an adjustable chin-rest was employed. All subjects saw the green after-image on every occasion. Five consecutive trials, with one-minute intervals, were performed. The criterion for the duration was the disappearance or breaking-up of the square-shaped outline of whatever colour. (Colour may change after the application of LSD). Previously it was found that duration decreases significantly in the order normals-neurotics-psychotics (7). Other attributes of the after-image, dealing with its rate of fluctuation, were looked for but not found to be present in all subjects.

The score was: *duration of the after-image in seconds*, as measured from termination of the exposure, averaged for the five trials.

(d) *Estimation of Quantities*. A set of 18 slides showing quantities of geometrical shapes such as circles, squares, etc., ranging from 12 to 30 in number, was exposed using a constant exposure time of 1/10 second. The exact method has been described earlier (7), and differs from the present situation slightly as regards the stimuli chosen. The subject is simply asked to guess how many items he has seen in an exposure. The relative over- or under-estimation was used as the score.

This test may not be as valid as the others in this battery for the following reasons. Firstly, the initial result that psychotics over-estimated relative to neurotics (7) was contradicted in two later experiments, using a total of eight heterogeneous test situations (13). Secondly, the latter experiments have shown the significance of results to depend largely on various conditions associated with the exposure, which are only superficially known.

The score was: *mean deviation of estimated quantities* from stimulus quantities, with signs of over- or under-estimation noted.

(e) *Figure Reconstruction Test (FRT), Immediate Recall*. This test has been described on a number of occasions (9, 14). A set of the immediate recall version, as used in the present experiment, consists of ten stimulus patterns, an example of which is shown in Figure 2. Each of these contains five shapes, a semi-circle, circle, triangle, square, and an oblong, spread about a central

reference point. Deviations in the drawn reproductions axial to this point are scored as "rotation error" and those radial to the central point as "distance error". Scoring is entirely objective.

From a series of experiments it is known that FRT error, whether measured under conditions of learning or recall, increases in the order controls-neurotics-psychotics (schizophrenics), differences being significant between any of these groups (6, 9, 12). Additionally, error was higher in normals after the administration of LSD, as against amytal (14). Such differences, as well as those between neurotics and schizophrenics, are only obtained with sufficiently long exposure times. This was kept constant at 15 seconds, as in the previous LSD-Amytal experiment, quoted above. At that time, 100  $\mu$ g. of LSD was used, compared with 60  $\mu$ g in the present experiment, which however may not always be sufficient to produce the desired effects. Two tests were given at any one session in order to increase reliability.

The scores were: *rotation error*, as measured by the mean degree of axial displacement of the individual shapes reproduced and *distance error*. The latter is scored in terms of the mean number of places by which reproduced shapes deviate radially from their stimulus position (described in 9).

(f) *FRT, Expressive Movement*. Reproductions of the FRT, described in the preceding section, may be scored for two types of movement characteristics: the actual size of the reproduced shapes and the distance from the central reference point at which the shapes are drawn. In differentiating between psychotics, or schizophrenics, on the one hand, and neurotics and normals on the other, measures of variability derived from the size score were the most successful, psychotics being most variable (11). Results for distance scores were in general poorer and are not considered. In the LSD-Amytal experiment, quoted above (14), variability was highest under the LSD condition, using a short exposure time (1/100 second). With long exposure, as employed in the present experiment, differences were much less pronounced. Nevertheless, by giving two tests after each injection, as against one in the LSD-Amytal experiment, it was hoped that the resulting increase of reliability would improve sensitivity of measurement to a useful degree.

The score was: *variability or standard deviation of size*, computed separately for the two tests given at each occasion, and then averaged. (With 10 reproductions of five shapes each, 50 measurements are computed per test.) Previously, variability was computed separately for "between" and "within" categories of shapes. As these two scores were consistently shown to yield similar results, the use of the standard deviation of size appears a justified choice and promises a more powerful combined score.

(g) *FRT, Recognition Certainty*. After administration of the recall portion of the FRT (Section e), one test set of 10 patterns was exposed rapidly, with an exposure time of one second per pattern. After that, subjects were shown a recognition card containing 30 patterns, including the 10 exposed patterns in a randomly balanced fashion. All patterns were similar so as to make correct identification extremely difficult. (For the present subjects, as well as for various groups of abnormals, correct judgment is in fact only slightly better than chance.) Firstly, subjects had to state for each of the 30 patterns whether they thought this pattern was likely to have been shown prior to recognition or not, as well as how certain they felt about their statement, using the following five degrees of certainty: very certain (+2), somewhat certain (+1), don't know (0), somewhat uncertain (-1), very uncertain (-2). The number of recognized items

per recognition card of 30 patterns is referred to as "*positive recognition*". Secondly, subjects were requested to pick out the ten patterns they were most certain of being the correct ones. For these 10 patterns the mean certainty score, derived from the first response, was computed and is referred to as "*degree of certainty*". The whole procedure was administered twice in succession in order to obtain satisfactory reliability. Measurement of degree of certainty has been discussed in detail elsewhere (10), the present method differing slightly, but not significantly, from the previous one for reasons of time economy.

As used in the present form, this recognition test is designed to create "unstructured", "ambiguous" situations known to facilitate the appearance of large individual differences in "response set". Scores are not measures of performance but of set, as those discussed in the first half of Section (b). The "degree of likes" score was, for strong empirical reasons, expected to vary with the scores discussed in the present section. On both positive recognition and degree of certainty, scores were found to be considerably higher for schizophrenics than for neurotics. These are being prepared for publication.

Scores used were: *positive recognition*, as the number of subjectively recognized patterns out of a total of 30, 10 of which having been shown prior to recognition and *degree of certainty*, or the mean degree of certainty, scored as ranging from -200 (-2 extreme) through +200 (+2 extreme), attached to the 10 patterns the subjects felt most certain of having recognized.

#### 4. Predictions for Psychological Tests

Equating LSD with psychotic test effects, the predictions for the ten scores proposed are listed below. Of these scores, numbers 1 and 3 are predicted from inference, all others on empirical grounds.

| Test Scores                   |    |    |    |    | LSD Score as<br>Against Placebo Score |
|-------------------------------|----|----|----|----|---------------------------------------|
| 1. J-A-H rating scale         | .. | .. | .. | .. | high                                  |
| 2. PRT degree of likes        | .. | .. | .. | .. | high                                  |
| 3. PRT response variability   | .. | .. | .. | .. | high                                  |
| 4. After-image duration       | .. | .. | .. | .. | low                                   |
| 5. Estimation of quantities   | .. | .. | .. | .. | low                                   |
| 6. Rotation error (FRT)       | .. | .. | .. | .. | high                                  |
| 7. Distance error (FRT)       | .. | .. | .. | .. | high                                  |
| 8. Size variability (FRT)     | .. | .. | .. | .. | high                                  |
| 9. Positive recognition (FRT) | .. | .. | .. | .. | high                                  |
| 10. Degree of certainty (FRT) | .. | .. | .. | .. | high                                  |

As stated in the discussion, personality tests in general have not been validated sufficiently to permit testing of specific hypotheses. As regards score 2, results between schizophrenics and other psychotics were similar. As to scores 4, 5 and 8 mixed groups of psychotics, though preponderantly schizophrenic, had been used. Scores 6, 7, 9 and 10 were investigated using groups of mixed paranoia and schizophrenia simplex only. On some of these scores, for example, 6 and 7, schizophrenics and psychotic depressives may react in a similar manner; on others, like scores 9 and 10, they may differ widely. Exact knowledge is, however, not available, which forces us to be satisfied with a rough test of the hypothesis proposed.



## RESULTS

Results are discussed in two sections according to their confirmatory or contradictory nature. They are presented in Figures 1 and 2 and Table I.

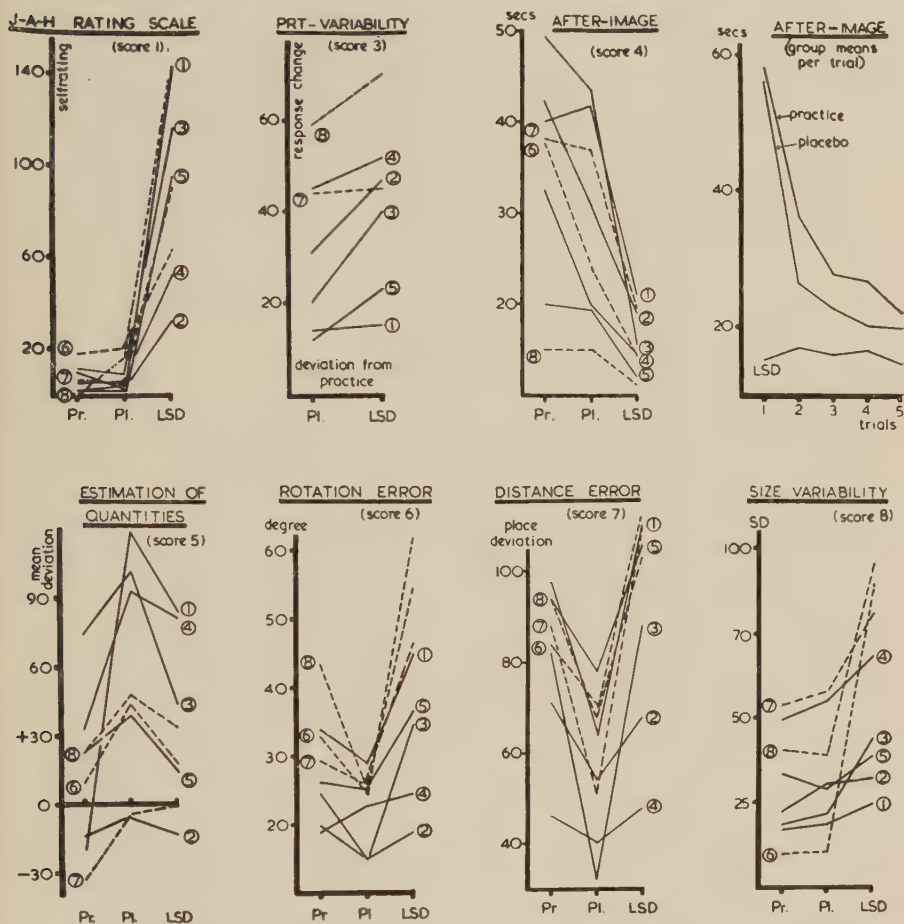


FIG. 1.—In all but one (subject 6, score 3), individual comparisons between placebo (Pl.) and LSD scores vary in the predicted direction. (Subject number encircled.)

1. *Results confirming the hypothesis.* Responses on seven of the ten scores used were found to vary in the predicted direction (Fig. 1). These results are significant as tested by the t-test (Table I). Out of 55 individual comparisons made—omitting subject 6 (score 3), whose LSD score was not obtained—54 agreed with the hypothesis and one was found to be contradictory (subject 7, score 5, assessment of quantities).

The conclusion may be drawn that, after the injection of a suitable dosage of LSD, normal responses vary in the direction of psychotic responses on a variety of extremely heterogeneous types of tests.

2. *Results contradicting the hypothesis.* Three scores did not confirm the hypothesis (Fig. 2; Table I, scores 2, 9 and 10) and an attempt is made in the discussion to find some reasons for this.

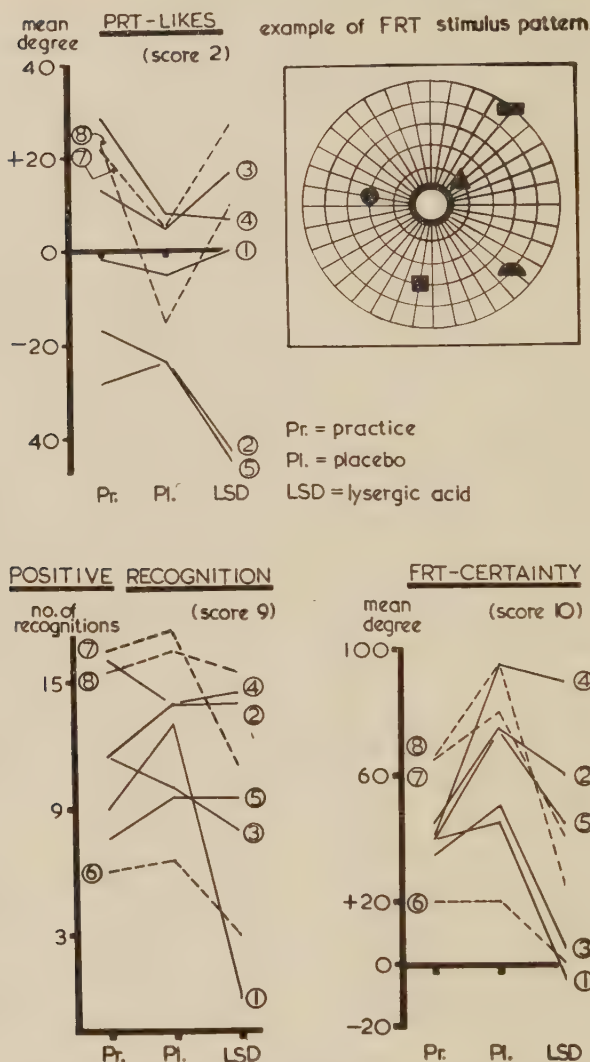


FIG. 2.—Three scores not confirming, or contradicting, the hypothesis. Example of a FRT stimulus pattern. Scoring grid, not present on test cards, is shown to facilitate understanding of scores (compare method sections e, f and g.)

As regards the degree of "likes" of abstract designs (PRT-likes, score 2), there was no discernible trend in either direction. In the case of positive recognition (score 9), only one out of the eight subjects increased his score to a slight degree, two stayed level and the rest decreased in part considerably. The critical ratio approached the 5 per cent. level of significance. Finally, as to FRT-certainty (score 10) all subjects contradicted the hypothesis and significance was highest with the exception of two other scores (1 and 7).

This appears to be the first instance in psychological LSD research that the hypothesis of psychotomimetic effects of LSD has been directly contradicted, as far as schizophrenic type of behaviour is concerned. Little can be concluded beyond this until the validity and generality of the present series of tests both as regards LSD and psychosis have been corroborated and extended.

TABLE I

*Difference Scores between Placebo and LSD Conditions and Their Significance*

| Difference Placebo—LSD |  |  | $\bar{X}$ | SD | t-ratio | Significance<br>(per cent.) |
|------------------------|--|--|-----------|----|---------|-----------------------------|
|------------------------|--|--|-----------|----|---------|-----------------------------|

|                         |    |    |         |        |        |           |
|-------------------------|----|----|---------|--------|--------|-----------|
| 1. Self-ratings         | .. | .. | 82.875  | 105.57 | 5.873  | 0.1       |
| 3. PRT-variability      | .. | .. | 8.375   | 19.69  | 2.756  | 2         |
| 4. After-image          | .. | .. | 13.000  | 21.82  | 4.460  | 0.5       |
| 5. Quantities           | .. | .. | 21.500* | 49.23  | 3.268  | 1         |
| 6. Rotation error       | .. | .. | 17.625  | 31.40  | 4.200  | 0.5       |
| 7. Distance error       | .. | .. | 36.250  | 48.96  | 4.988  | 0.5       |
| 8. Size variability     | .. | .. | 26.625  | 71.88  | 2.772  | 2         |
| 2. PRT-likes            | .. | .. | 3.875   | 36.89  | 0.681† | N.S.      |
| 9. Positive recognition | .. | .. | 3.250   | 12.47  | 1.951† | N.S. (10) |
| 10. FRT-certainty       | .. | .. | 34.375  | 55.87  | 4.604† | 1         |

Df. = 7.

\* Computed to one decimal (compare Fig. 1).

† 2-tail tests. All others 1-tail tests.

### DISCUSSION

At the present rudimentary stage of personality test development, a satisfactory test of the alleged psychotomimetic effects of LSD is very difficult to perform at the psychological level. There are no tests with acceptable norms specific to psychosis and the various psychotic subgroups, whether clinical or psychological, to serve as reliable indicators of the degree of the behavioural responses in question. An approximation to this aim may be demonstrated in the following, using two scores derived from the Figure Reconstruction Test.

| <i>Experiments</i>                |    |    |    | <i>FRT Rotation<br/>Error<br/>(mean degree)</i> | <i>FRT Size<br/>Variability<br/>(SD per set)</i> |
|-----------------------------------|----|----|----|-------------------------------------------------|--------------------------------------------------|
| 1. Present experiment:            |    |    |    |                                                 |                                                  |
| (8 normals, placebo condition)    | .. | .. |    | 22.8                                            | 32.6                                             |
| 2. Previous experiment:           |    |    |    |                                                 |                                                  |
| (48 neurotics)                    | .. | .. | .. | 23.7 (12)                                       | 27.1*                                            |
| 3. Previous experiment:           |    |    |    |                                                 |                                                  |
| (24 schizophrenics)               | .. | .. | .. | 31.8 (12)                                       | 35.3*                                            |
| 4. Present experiment:            |    |    |    |                                                 |                                                  |
| (8 normals given 60 $\mu$ g LSD)  | .. | .. |    | 40.7                                            | 59.2                                             |
| 5. Previous experiment:           |    |    |    |                                                 |                                                  |
| (6 normals given 100 $\mu$ g LSD) | .. | .. |    | 44.7 (14)                                       | —†                                               |

\* Results in preparation for publication.

† Not computed as a different measure of size variability was used.

From this it may be seen that normals given LSD not only vary in the direction of schizophrenic test response—regardless whether the scores of neurotics are consonant or dissonant with this direction—they also may be assessed as to the degree of this variation using the existing experimental norms. It is noted thereby that the LSD response exceeds the schizophrenic mean by far. Considering the medium dose of 60  $\mu$ g LSD only, four (16.7 per cent.) of the 24 schizophrenics scored higher than the rotation error mean and a mere three of them (12.5 per cent.) exceeded the respective size variability mean of the LSD group. The extent of the differences between LSD (Experiment



4) and schizophrenics (Experiment 3), though agreeing in direction, appears surprising and should be considered in weighing up the evidence for the nature of LSD effects.

As regards the discrepant results obtained with test scores 2, 9 and 10, the following suggestions are offered. Firstly, if the significant contradiction (score 10) of the hypothesis that LSD responses in normals correspond to those of schizophrenics without LSD is a true result, one more suggestion is adduced to support the drug specificity hypothesis. Secondly, it may be argued that the three scores in question are all of one particular type of response ("response set") and represent a specific deviation from an otherwise general rule. Thirdly, it is possible that "response set" of this kind is, in contrast to schizophrenics, low in other psychotics, for example, in manic-depressives. This would permit the hypothesis of correspondence between LSD effects and psychosis being upheld in a more specific manner.

In analysing test scores 2, 9 and 10 in greater detail, one is struck by the widely differing levels of significance, with critical ratio varying from 0.681 to 4.604, despite the fact that all three scores have been found to differentiate in a highly significant manner between schizophrenics and other groups. This may provide a key to differential effects in test attitude of normals, mediated by test conditions, which do not operate in abnormals. Quoting again from own experiments, being written up for publication, it was found that schizophrenics may "rigidly" maintain a high level of certainty (score 10) in FRT performance, despite varying task conditions, whereas neurotics varied more significantly. The suggestion may be derived that schizophrenics score relatively equally high on three measures of "response set", where between-test differences of normals are considerably higher. In other words, schizophrenics, varying less with task conditions, have "lost a certain amount of insight" in external stimulus conditions, whereas the set of normals corresponds more closely to such conditions, one of which may be difficulty of task. Applied to the present discussion, score 2, where a judgment of likes of abstract designs is called for, involves little effort on the side of the subject, whereas score 10 (FRT-certainty) requires a response to a difficult task of discriminating from memory between highly similar patterns. If normals given LSD, in contrast to schizophrenics, react by decreasing their certainty with difficulty of performance—or whichever other factor may be responsible—it may be assumed that no true schizophrenic condition developed because "insight in difficulty of performance was retained". As a result of injection of LSD, memory performance decreases significantly and confidence in performance drops accordingly in normals.

The suggestion that, depending on the degree of difficulty, response set varies as a result of the LSD injection rather than a "psychotic reaction" receives some support from a previous experiment (10), where the same test (FRT) was used in a rather similar manner. Certainty was investigated under two conditions varying in difficulty, though possibly also in other respects. It was stated that "differences in degree of certainty, as found between recall (=easy task) and recognition (=difficult task) may be due to corresponding differences in levels of difficulty". With the easy task certainty decreased in a "dimensional" fashion in the order amytal-placebo-d-amphetamine. With the difficult task certainty decreased in the order placebo-amytal-d-amphetamine. This comparison affords a certain amount of corroboration to the assumption of drug specificity, in two ways. Firstly, both the d-amphetamine and the LSD, one—under the conditions employed—a "non-psychotizing", the other a

"psychotizing" drug, appear to exert a similar influence on certainty. Secondly, provided the task is "difficult" enough, heterogeneous drugs will, in normals, have a similar effect. (The term "difficulty" should be taken as provisional. Although it is certain to be one important experimental variable in the present context other conditions like "insight in task conditions", or "degree of structure", and "felt" as against "objective" difficulty, may prove of equal importance.)

Lastly, it may be mentioned that trial analysis of the after-image test (Fig. 1) revealed differences to be greatest at the first trial and to decrease with practice. This parallels the previous finding, that differences between normals, neurotics and psychotics were more significant for a first than for a second trial (7). The knowledge of this result may be helpful in the design of future test procedure and interpretation.

#### SUMMARY

The hypothesis was tested that LSD-treated normals react in the same way as psychotics (?schizophrenics) in a series of tests previously validated against the normal—psychotic, or neurotic—psychotic dichotomy. Confirmation of the hypothesis would tend to strengthen the assumption that LSD produces in normals a psychotic-like reaction, that is one in which all the measurable characteristics are also found in the clinical psychoses, particularly schizophrenia.

In fact, confirmation was only obtained in seven out of the ten scores of self-rating, perceptual variability, duration of the negative after-image, estimation of quantities, two types of immediate recall error, and variability in size of certain drawings. The remaining three scores were of "response set". In the case of two of these (measuring likes of abstract designs and generalization in recognition) the hypothesis was not confirmed, and in the other (certainty in recognition) it was definitely contradicted. The discussion favoured interpretation of these results as supporting a drug rather than a disease oriented theory of LSD action.

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# ALLEVIATION OF THE PSYCHOLOGICAL EFFECTS OF LSD IN MAN BY 5-HYDROXYTRYPTOPHAN

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## INTRODUCTION

IN the investigation described, the hypothesis was tested that 5-hydroxytryptamine (5HT) acts to reduce the psychological effects of lysergic acid diethylamide (LSD). The method was to inject 5-hydroxytryptophan (5HTP) prior to LSD and to compare the results of psychological tests performed after these injections. Placebo controls were used.

Gaddum (1953b) noted that LSD was an effective antagonist to the action of 5HT on the peripheral tryptamine receptors of smooth muscle (Gaddum, 1953a). From this arose the concept that a central antagonism to 5HT might account for the psychological properties of LSD (Amin *et al.*, 1954). Other work, however, suggests that LSD may act on the mental state by potentiating 5HT. Costa (1956) reported that, in small doses, LSD potentiated the action of 5HT on rat uterus and further evidence suggesting that LSD has a 5HT-like effect has been provided by other authors in electrical studies on the experimental animal (Marrazzi and Hart, 1955; Rinaldi and Himwich, 1955). On the other hand Cerletti and Rothlin (1955) have doubted whether 5HT plays any part in inducing the LSD psychosis. The position has been further clouded by the description of an LSD-like effect following administration of 5HT in high dosage in the experimental animal (Udenfriend *et al.*, 1957; Woolley *et al.*, 1957).

Evidence provided by two other groups of workers, although difficult to interpret, deserves to be considered (Isbell and Logan, 1957; Taeschler and Cerletti, 1957). They reported that reserpine, given 20 hours before LSD, greatly increased its psychological effect. In their paper, Isbell and Logan suggested that LSD was potentiated by free 5HT released from its binding sites by reserpine. In the opinion of the present authors the converse is more likely for it has been shown that 5HT, so liberated, is rapidly destroyed by monoamine oxidase (Brodie *et al.*, 1955; Sjoerdsma *et al.*, 1955), and there is a resultant lack of readily available 5HT. This depletion may provide an explanation for the phenomena observed by these authors. It may be that a lack of readily available intracellular 5HT, normally perhaps liberated steadily in

receptor regions during LSD challenge (Brodie *et al.*, 1957) results in an enhanced LSD reaction.

We suggest that a central antagonism between LSD and 5HT is the correct interpretation of observed phenomena. If this were so, an increase in readily available 5HT might be expected to attenuate the LSD response. This hypothesis may be tested, since a means of increasing brain 5HT is now known. In the experimental animal Udenfriend and his colleagues (1957) have observed that, although parenterally administered 5HT did not cross the blood brain barrier, its precursor, 5HTP, gains free access to the brain to be decarboxylated *in situ* to 5HT. As the pharmacological effects of 5HTP broadly parallel the concentrations of 5HT, it is likely that 5HTP acts through its conversion to 5HT. Thus it is likely that, by giving 5HTP, the amount of readily available 5HT in the brain is increased in man also.

## METHOD

1. *Subjects and drug administration.* Normal volunteers with an age range of 25 to 31 years were given 60  $\mu$ g of LSD in 10 ml. water intravenously. Injections took place on two occasions, preceded either by 25 mg. of DL-5HTP in 5 ml. solution or an equivalent volume of placebo. The latter two injections, administered on subsequent days, were randomized using a balanced design so as to avoid sequence effects. Neither the subjects nor the psychologist knew, until he had scored the results, whether 5HTP or placebo had been given.

2. *Test administration.* Specimens of urine were collected for estimation of 5HT and its major metabolite 5-hydroxyindoleacetic acid (5HIAA). 5HT was estimated colorimetrically by the method of Udenfriend *et al.* (1955a) and 5HIAA by that of Udenfriend *et al.* (1955b). Two dimensional urinary indole chromatograms were obtained by the method of Jepson (1955) and the identity of 5HT was confirmed by its fluorescence characteristics (Jepson and Stevens, 1953). A Lloyds reagent adsorption method was employed for urinary creatinine (Hare, 1950).

After a timed specimen of urine had been collected, the subject was given an intravenous injection of either 25 mg. 5HTP in 5 ml. solution or an equivalent amount of placebo. Thirty minutes later he was given the battery of psychological tests. When this was completed and 90 minutes after the initial injection, the subject was asked to empty his bladder and 60  $\mu$ g of LSD in 10 ml. water was given intravenously. Thirty minutes later the psychological tests were repeated and urine collected on completion of the tests. After one day's interval the investigation was repeated, alternating the 5HTP with the placebo. Care was taken that the time of day and the interval between tests were kept constant.

3. *Psychological tests.* Brengelmann (2), using the present subjects, has shown that the following tests vary consistently and in the predicted direction with LSD compared to placebo; for detailed information the reader is referred to this paper. These scores may therefore be used to assess the effect of 5HTP on the psychological properties of LSD.

| Test Scores                                                                                           | LSD Score as<br>Against Placebo Score |
|-------------------------------------------------------------------------------------------------------|---------------------------------------|
| 1. <i>J-A-H rating scale:</i> response to physiological, perceptual and cognitive questions . . . . . | high                                  |

- 2. *PRT response variability*: variability in the degree of like of abstract design .. .. . high
- 3. *After-image duration*: duration of the negative after-image of a red square .. .. . low
- 4. *Estimation of quantities*: assessment of the number of geometrical shapes, ranging from 12 to 30 in number .. .. . low
- 5. *Rotation error (FRT)*: error in reproducing the position of visually exposed stimuli (immediate recall) .. .. . high
- 6. *Distance error (FRT)*: as under 5 .. .. . high
- 7. *Size variability (FRT)*: variability in the size of stimuli reproduced by drawing (expressive movement) .. .. . high

The tests were given one day before the first injection in order to control for practice and to familiarize subjects with the situation. Randomizing orders A and B of tests and injections over the subjects taking part, the following basic schedule was employed. Testing started 30 minutes after each injection and was completed within the next hour.

|   |    |     | First Day | Second Day  | Third Day   |
|---|----|-----|-----------|-------------|-------------|
| A | .. | ... | Practice  | 5HTP-LSD    | Placebo-LSD |
| B | .. | ..  | Practice  | Placebo-LSD | 5HTP-LSD    |

RESULTS

The experiment is reported in an unfinished state due to the severe reaction of one of the volunteers after his first LSD injection which had followed 50 mg. of 5HTP. Although the reaction cleared after two days, the experiment was discontinued. Although only five subjects completed the tests, the results are sufficiently suggestive to warrant publication.

1. *Clinical findings*. Apart from mild nausea in one subject, no clinical effects were observed in the 90 minutes following injection of 5HTP, nor could any uniform change in the LSD psychosis be observed when the effect of placebo and 5HTP were compared. Subjects, when asked at the end of the

TABLE I  
*The Levels of 5-Hydroxyindoleacetic Acid (5HIAA) and 5-Hydroxytryptamine (5HT) in the Urine of Normal Volunteers Before and After Intravenous Injection of 25 mg. of 5-Hydroxytryptophan (5HTP) or Placebo*

|         |        |            | 5HTP    |          |           | Placebo |          |           |
|---------|--------|------------|---------|----------|-----------|---------|----------|-----------|
|         |        |            | 0 mins. | 90 mins. | 180 mins. | 0 mins. | 90 mins. | 180 mins. |
| Case 1: |        |            |         |          |           |         |          |           |
| 5HIAA   | mg./g. | Creatinine | .. 1.7  | 23.6     | 2.8       | 2.4     | 3.8      | 9.6       |
| 5HT     | mg./g. | Creatinine | .. 0.6  | 10.6     | 3.3       | —       | —        | —         |
| Case 2: |        |            |         |          |           |         |          |           |
| 5HIAA   | mg./g. | Creatinine | .. 6.9  | 31.4     | 8.1       | 2.0     | 2.1      | 1.25      |
| 5HT     | mg./g. | Creatinine | .. 0.9  | 9.4      | 3.5       | —       | —        | —         |
| Case 3: |        |            |         |          |           |         |          |           |
| 5HIAA   | mg./g. | Creatinine | ... 2.6 | 20.6     | 8.1       | 1.6     | 2.1      | —         |
| 5HT     | mg./g. | Creatinine | .. 3.6  | 8.6      | 1.0       | —       | —        | —         |
| Case 4: |        |            |         |          |           |         |          |           |
| 5HIAA   | mg./g. | Creatinine | .. 7.3  | 16.8     | 9.4       | 8.9     | 11.5     | 3.2       |
| 5HT     | mg./g. | Creatinine | .. 0.8  | 7.2      | 1.9       | —       | —        | —         |
| Case 5: |        |            |         |          |           |         |          |           |
| 5HIAA   | mg./g. | Creatinine | .. 3.9  | 28.5     | 12.5      | 2.8     | 7.6      | 3.2       |
| 5HT     | mg./g. | Creatinine | .. 0.0  | 11.8     | 9.7       | —       | —        | —         |



experiment, could neither distinguish between placebo and 5HTP, nor between placebo-LSD and 5HTP-LSD conditions, although their self-ratings on the J-A-H rating scale varied consistently with the latter two conditions. The only consistent and already well known self-observation was that the severity of a number of LSD effects decreased with the second injection.

2. *Biochemical results.* Intravenous injection of 5HTP was followed by a characteristic urinary chromatographic pattern dominated by three major 5-hydroxyindole spots, 5HTP (presumably to a large extent the unchanged D-isomer), 5HT and 5HIAA. These findings were confirmed by quantitative

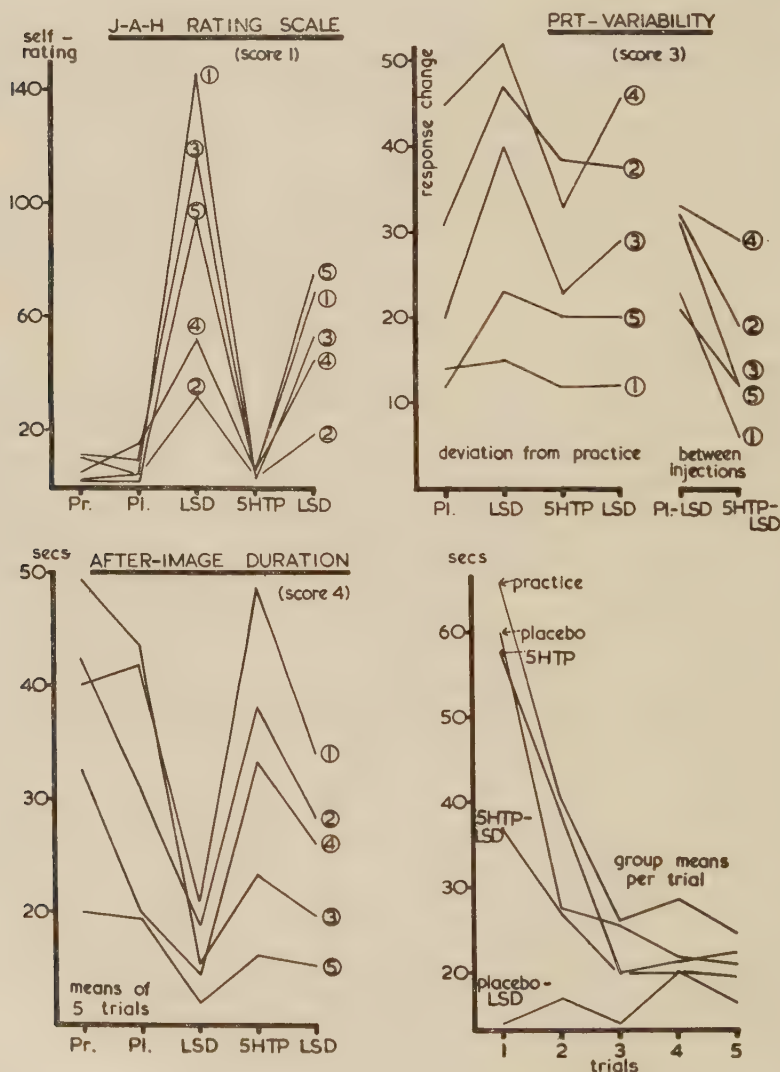


FIG. 1A.—Normalizing effects of 5HTP on the LSD reaction: reduction of self-rated disturbances (score 1) and variability in perceptual responses (score 3), and increase in duration of the negative after-image (score 4). Differences for the latter score decreased with practice. (Subject number encircled.)

Pr.—Practice. Pl.—Placebo. LSD=lysergic acid. 5HTP=5-hydroxytryptophan.

studies which also served to demonstrate that 5HTP was being metabolized during the period of the experiment (Table I).

3. *Psychological results.* 5HTP, alone, did not affect the psychological test scores.

Comparing LSD following placebo, with LSD following 5HTP, it is found that 5HTP appears to reduce the LSD effect in every one of the seven scores, so far as the group means are concerned (Table II). Of 35 *individual* comparisons, made for these seven scores and five subjects each, this rule holds in 33 instances, the exceptions being subject 1 for the estimation of quantities and subject 2 for distance error (Fig. 1).

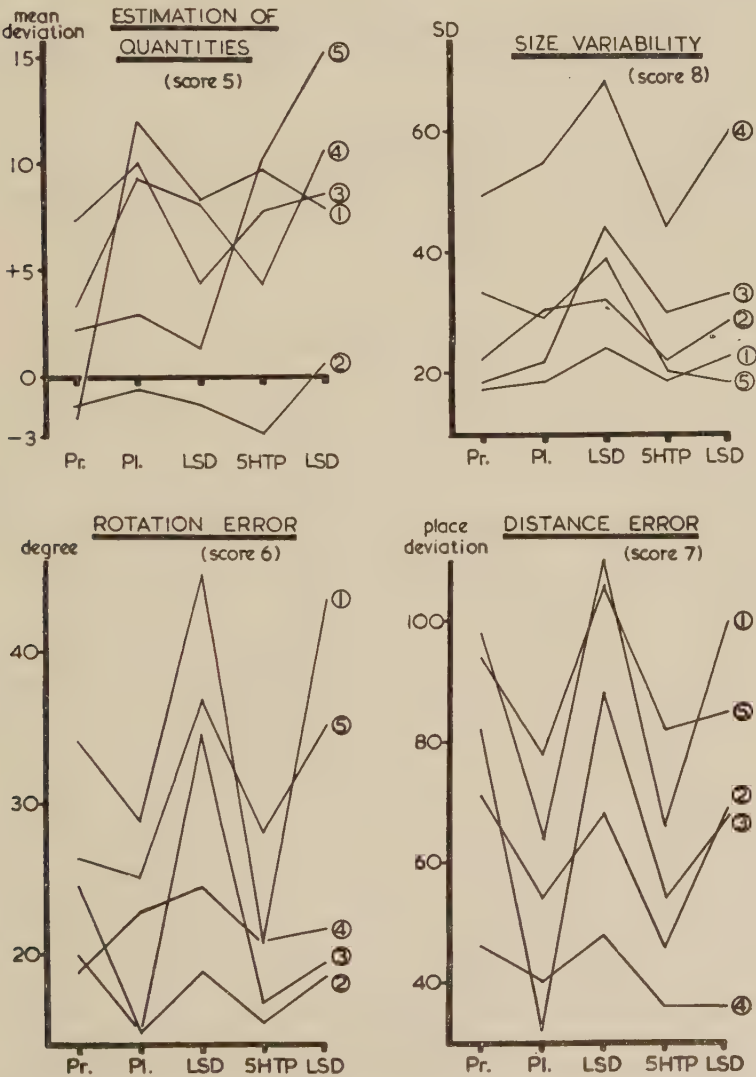


FIG. 1B.—Normalizing effects of 5HTP on LSD: tendency towards increase in estimated quantities (score 5), decrease in expressive movement (score 8) and of immediate recall error (scores 6 and 7.)

If the more severe test, demanding the post-5HTP/LSD means to fall between the placebo and post-placebo LSD levels, is applied, the result is positive for all scores concerned with the exception of estimation of quantities. Considering the individual responses for this test (Fig. 1), the rule is followed in all five cases for the J-A-H rating scale (score 1) and the after-image duration (score 4), in four out of five cases for FRT response variability (score 3) and rotation error (score 6), and in three out of five cases for distance error (score 7) and size variability (score 8).

Within the limits of the present conditions, the suggestion may be derived that 5HTP reduces the effects of the LSD reaction.

TABLE II  
*Group Means of Five Subjects Who Finished all Tests*

| Means of 5 Subjects          |       | Practice | Placebo | LSD  | 5HTP | LSD  |
|------------------------------|-------|----------|---------|------|------|------|
| 1. J-A-H rating scale        | .. .. | 6.0      | 4.8     | 87.6 | 6.2  | 52.4 |
| 3. PRT response variability* | .. .. | —        | 24.4    | 35.4 | 25.2 | 28.8 |
| 4. After-image duration      | .. .. | 36.9     | 31.2    | 16.4 | 31.8 | 24.7 |
| 5. Estimation of quantities  | .. .. | 19.2     | 69.2    | 42.0 | 59.0 | 86.0 |
| 6. Rotation error (FRT)      | .. .. | 24.7     | 21.2    | 31.9 | 20.2 | 27.7 |
| 7. Distance error (FRT)      | .. .. | 78.4     | 53.6    | 84.0 | 56.8 | 71.6 |
| 8. Size variability (FRT)    | .. .. | 28.1     | 30.9    | 41.6 | 27.1 | 32.7 |

\* No score for practice, as deviation from practice is scored.

#### DISCUSSION

In the last few years evidence has been accumulating that 5HT plays a vital role in normal brain functioning and this evidence has recently been reviewed by Gaddum (1956). The proposition that some psychiatric disorders, such as schizophrenia, may be related to a disturbance of 5HT metabolism (Woolley and Shaw, 1954) is, however, based on slender grounds. This concept arose by analogy with the 5HT-antagonism displayed by many of the hallucinogens in experiments on smooth muscle. But there has been no direct support for a central antagonism and it is here that the present investigation is of interest.

To minimize the risk of undesirable peripheral side effects, small doses only of 5HTP were used. Because of this it was not surprising that a crude clinical assessment failed to demonstrate any gross effect of 5HTP on the LSD psychosis. Psychological tests however showed that, although 5HTP alone had no demonstrable effect on the mental state in this dosage, it resulted in a definite reduction of the psychological effect of LSD. As only five subjects completed the tests, the results cannot be regarded as conclusive although the wide areas covered by these tests and the uniformity of results compensate to some extent for the small number of cases. They support the hypothesis that 5HT is related to the LSD psychosis and that this relationship is one of antagonism between 5HT and LSD.

It was noted by Udenfriend *et al.* (1957) that large doses of 5HTP resulted in LSD-like effects in the experimental animal and a similar observation has been made by Woolley and his colleagues (1957). At first sight this would appear to suggest that LSD potentiates 5HT. However, it must be remembered that the enormous dosage of 5HTP administered by these workers, about 100 times that used here, may have a pharmacological action qualitatively different from the drug when given in amounts approaching the physiological. Certainly there was no evidence, clinically or on psychological testing, that



5HTP alone, in the dosage used in the present investigation, affected the mental state.

Finally, the urinary 5-hydroxyindole partition pattern following 5HTP injection is itself of interest. Our findings confirm data, published by Davidson *et al.* (1957) while this paper was in preparation, that comparatively large amounts of 5HT as well as 5HIAA are found in the urine. Parenteral administration of 5HT results almost entirely in the excretion of 5HIAA alone (Erspamer, 1956; Udenfriend *et al.*, 1956; Davidson *et al.*, 1957).

#### SUMMARY

The hypothesis that excess brain 5-hydroxytryptamine (5HT) will reduce the psychological effects of lysergic acid diethylamide (LSD) has been tested and confirmed, using psychological tests for measurement. Normal subjects were given LSD on two occasions, the LSD being preceded on one occasion by 5-hydroxytryptophan (5HTP) and on the other by placebo. Urinary 5-hydroxyindole partition studies were used to demonstrate that 5HTP was being metabolized throughout the experimental period; a characteristic pattern is described.

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## Reviews

**Mental Depressions and Their Treatment.** By SAMUEL HENRY KRAINES, M.D. The MacMillan Company, New York, 1957. Pp. 555.

Dr. Kraines claims that his approach to the study of manic-depressive illness is eclectic, but this does not prevent his coming down firmly on the side of primary physiopathology as a *sine qua non* in the causation of this condition. In short, people suffer from manic-depressive illness, its phases or its variants, because they are made that way. Psychological factors are deemed to modify, complicate and perhaps prolong symptoms which spring from a physiological disturbance which is itself due to a combination of hereditary susceptibility, and a physiological, possibly a hormonal, trigger. Many psychiatrists share this view, though not all of them would find it easy to state concisely the grounds on which they support it.

The bulk of the book is clinical description, with numerous quotations from case-records, and a detailed analysis of variations in course and of groups of symptoms.

In an appendix (29 pages), Dr. Kraines elaborates a theory of causation, based on the general body of physiological knowledge that has accumulated during, roughly, the present century. Briefly, this is that the mechanism of the illness is a (usually) reversible disturbance of function in the diencephalic area, including the thalamus, hypothalamus, reticular system and rhinencephalon. As to the nature of the morbid process, the author is less positive. He suspects that in many patients "... gonadal pathology is aetiologic", but he is not prepared to exculpate "... circulatory changes, nutritional inadequacy, metabolic instability, toxic factors and any other phenomenon which may disturb the functions of the centrencephalic systems ...". These conjectures, which may evoke nostalgic recollections in the minds of some older readers, lead the author to declare: "Thus, though the symptoms of the manic-depressive disease, funneled through common mediating mechanisms, may appear similar in most cases, the specific aetiologic factor may differ. Ideal therapy is dependent on determining the exact cause; someday, searching, we shall find the origin and the cure." Trite though this is, the book is worth reading; for Dr. Kraines has brought together a great deal of knowledge of the literature on the one hand and an obviously extensive and keenly perceptive clinical experience on the other. The latter enables him to give excellent, clearly defined descriptions, especially of the less abundantly recorded variants of the illness, with prominent somatic complaints, that are so frequently seen in out-patient practice, and to provide a concise, practical account of treatment. If, as some might consider, he seems to make things more cut and dried than they really are—and this is emphasized by his leaning towards tidy little theoretical diagrams—he will at least make the thoughtful clinician want to brush up his physiology; and maybe workers in some of the ancillary scientific departments will be stimulated to make specific experimental enquiries. But we still have a long way to go.

IAN SKOTTOWE.

**The Subnormal Mind.** By SIR CYRIL BURT, D.Sc., Hon.Litt.D., Hon.LL.D. Oxford University Press, London, 1955. Third edition. Pp. xix+391.

When people speak of medical psychology, one is apt to think of Freudian, Jungian or Adlerian psychopathology—or some of their now numerous derivations. It is well to realize that just as psychiatry has been called, rather hyperbolically, the other half of medicine, so there is another half, as it were, of medical psychology, though in this case the metaphor is less of an over-statement. In the practical field, a considerable proportion of this other half is concerned with the study and assessment of such attributes as mental ability, learning capacity, social surveys of behaviour as



an index of trends in the development of character in selected populations. In short, the domain of mental tests, statistics, experiments, educational psychology and the like is of no less practical importance, especially in the management of psychiatric problems in children, than the more esoteric realm of luxuriant psychopathology; but it is a good deal more exacting to apply. It embodies a down to earth discipline, concerned more with what is actually happening in the daily lives of children, and with what is to become of them, than with intriguing speculations of the relevance of past experience, individual or collective.

In this practical field, Sir Cyril Burt's work is outstanding in this country, and his Heath Clark Lectures (1933) from which this book is derived remain a unique pioneer's presentation of the subject, even today. The author scrutinizes and gives his views, based on a vast experience, about mental deficiency, backwardness, delinquency and neurosis, in a most readable manner and one that makes a strong appeal to innate commonsense. He has his own foibles—who among original researchers has not?—and if he uses expressions like “sthenic neuroses” and “asthenic neuroses”, which are today strange to ordinary psychiatrists, at least his descriptions leave no doubt about what he means by them; but he is rather given to footnotes, some of inordinate length.

There is a good introductory chapter on the normal mind which throws up in sharp contrast those on subnormal and other abnormal states that follow. An appendix includes valuable details of tests and a questionnaire on neurotic symptoms. The bibliography is adequate.

One gets the impression that in this edition the author contrives to keep his readers up to date, without losing the characteristic flavour of the original work. He is by no means mechanistic in his outlook; on the contrary, his technical studies are clearly made upon a background of broad human understanding, and they surely go a considerable way to achieving one of the implied objectives of a work such as this—human enlightenment.

This book continues to be a desirable inclusion for the library of every place, medical, educational, and administrative, that has a hand in the psychiatry of children.

IAN SKOTTOWE.

**Recent Advances in Neurology and Neuropsychiatry.** By SIR RUSSELL BRAIN, Bt., M.A., D.M., P.R.C.P., and E. B. STRAUSS, M.A., D.M., F.R.C.P. J. & A. Churchill, Limited, London, 1955. Pp. 311. Price 30s. Sixth edition.

The appearance of a new edition of this work will be welcomed by senior clinicians who want to keep themselves up to date with solid advances, but who can ill spare the time to sift grain from chaff, and by junior specialists in training who are preparing for special examinations in neurology and psychiatry or higher examinations in general medicine.

The subject matter has been revised and expanded to include diverse syndromes—for example, carcinomatous neuropathy, the carpal tunnel syndrome, Coxsackie disease and portal-systemic encephalopathy—that have received special attention or original notice in the past ten or twelve years. Advances in treatment, too, are briefly described, including the relevance of antibiotics and the modern drug treatment of epilepsy; but the tranquillizing drugs are not discussed.

Dr. Denis Hill now contributes a chapter on electro-encephalography, and Dr. David Sutton one on neuroradiology, both of them well illustrated. Mr. Douglas Northfield writes a brief chapter on intracranial tumours.

The authors remain true to the principles they adopted in the first edition, namely, that all subjects treated should have a clinical bearing and that the book should be an auxiliary text-book of applied neurology containing selected material and references (the latter continue to be extremely well chosen) with no claims to comprehensiveness. In the light of this pronouncement, the reader will not cavil at the predominance of neurological over psychiatric matter. On the contrary, the

practising psychiatrist will be grateful to find a high degree of relevance to his specialty in the authors' selection and presentation of their material. In short, a psychiatrist is likely to learn more about neurology than a neurologist could learn about psychiatry from this work. With advancing knowledge, the territory common to both these aspects of medicine is expanding and conceptual distinctions of specialties are less important than the sharing of knowledge to the general advantage. One ventures to hope that it may be thought that psychiatry and psychology could have a little more to offer in future editions. An account of advances in knowledge of the higher functions of the nervous system, especially in relation to the clinical fields of electro-encephalography and cerebral surgery, might well be accompanied by, for instance, an account of advances in the testing and, where practicable, the measurement of those functions. It is usual in many centres for detailed psychological testing to precede such operations as leucotomy, especially the surgically limited varieties of it, as well as hemispherectomy and partial lobectomy; and much can be learned from applying such tests to patients with cerebral tumours and other gross lesions. Not only are they of immediate clinical value but they provide yet another opportunity for operational research; an account of them would be in line with the principles of this excellent work and might further enhance its value.

IAN SKOTTOWE.

**The Psychology of Abnormal People.** By JOHN J. B. MORGAN, Ph.D., and GEORGE D. LOVELL, Ph.D. Longmans, Green and Co., London. Second edition. Pp. 673; figs. 20. Price 35s.

This is a psychological rather than a psychiatric book, though it deals in part with mental disorders, including psychoneuroses, schizophrenia, manic-depressive illness and organic disturbances, and with psychotherapy. In the authors' words, it is intended "... to interest students in abnormal behaviour so that they may both (*a*) understand abnormal people better and (*b*) understand some of their own abnormal behaviour through seeing exaggerations from the normal in bold relief". They take the view that knowledge of this kind is part of the culture of an educated citizenry, so they use plain English wherever they can and they include a glossary of technical terms. But they make it clear that an introductory course in general psychology is a desirable pre-requisite to a study of their book.

The tone of the book may be misjudged from the title of the first chapter: "How to understand Unusual Persons". The authors go straight to the heart of their subject before turning to a more conventional presentation of it, step by step, in chapters on disorders of intelligence, sensation, perception, association, memory and emotion. They then pass into the clinical field, about two-thirds of the way through the book. A psychobiological and psychodynamic orientation—by no means overdone—is suitably blended with less personal, more scientific, material. Despite the initial aura of informal and easy exposition, this is by no means a shallow, "popular" work in the sense of "psychology for the masses", or anything of that kind. It is in fact a serious exposition in a very readable form of a substantial part of the practical and clinical psychological fields by authors whose scientific and academic standing is impeccable and who know how to formulate their material for an educated laity without losing the constantly recurring stimulus of something new and interesting to be found in the next chapter.

References are well chosen and abundant, and in the clinical chapters the authors rightly draw freely on the established works of acknowledged leaders in that field; and they contrive to present the gist of them in a balanced and realistic way.

This book would make excellent background reading for clinical psychologists, social workers and, indeed, for psychiatrists who are open-minded enough to be interested in someone else's outlook on their work; and it would serve as helpful additional introductory background reading for the junior specialist in training—to be taken in leisurely stages. If it has a fault it is that, in Britain at any rate, it might be considered rather too long and rather too full of information for its primary

purpose—to educate the layman. But this probably stems from cultural differences between ourselves and our opposite numbers in the country of its origin. It is a well-informed, balanced, well-written work.

IAN SKOTTOWE.

**The Neurological Basis of Behaviour.** Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME, M.B., and CECILIA M. O'CONNOR, B.Sc. J. & A. Churchill, Ltd., London, 1958. Pp. 400, with 109 illustrations. Price 52s. 6d.

The book contains nineteen papers contributed by members of the Symposium. Thirty-four members took part, including many of the leading workers in neurophysiology and its related subjects.

The volume is one of the now well known Ciba Foundation Symposia, and little more need be said than that it sustains their usual standard. The emphasis is heavily on the neurophysiological, and the "behaviour" discussed in the articles seldom rises above the reflex. Behaviour as it is understood by the psychiatrist is at present hardly within the view of those whose main interest is neurophysiological. Nevertheless, the book can be recommended as a good survey of the position in 1958.

W. ROSS ASHBY.



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#### *Recent Memory Impairment in Unilateral Temporal Lesions*

Four cases of temporal lobectomy are presented to illustrate the type of memory defect which may occasionally follow such lesions.

The amnesia is characterized by severe impairment of recent and little involvement of remote memory.

The explanation of the rarity of this complication is discussed.

The anatomical basis would seem to be local cortical, possibly hippocampal, damage rather than interruption of afferent or efferent tracts from the medial temporal structures.

(Author's Abstr.)

#### *Studies on Effect of the Injection of Alumina (Aluminum Oxide) Cream into the Basal Ganglia*

A standardized preparation of alumina (aluminum oxide) cream was injected into various subcortical nuclei in 16 monkeys, in amounts known consistently to produce seizures when placed on the motor cortex.

The animals were observed and serial electroencephalograms recorded, employing pentylene-tetrazol U.S.P. (Metrazol) activation over a period of from 5 weeks to 14 months (average 7 months).

There were no spontaneous seizures. Eight animals developed spontaneous electroencephalographic alterations, and four demonstrated some increased sensitivity to pentylene-tetrazol-induced seizures.

On histological study the lesions were found to lie in most of the principal basal ganglia and thalamus.

(Authors' Abstr.)

#### *Depressive Affect and Endocrine Functions*

The mean hydrocortisone levels of depressed patients are elevated as compared with levels for normal controls. Protein-bound iodine levels are also elevated, but not significantly.

In general, the more emotional distress the patient is undergoing, the higher the hydrocortisone level. There is a significant relationship between those patients who are suffering intensely, are retarded, and unable to cry, and those who are less depressed, agitated, and crying. The hydrocortisone levels parallel this relationship, the most intensely depressed and retarded group having distinctly higher levels than the less depressed group.

A correlation matrix of the first occasion is presented to demonstrate existing relationships among subgroups of the study.

The multiple correlation indicates that (a) the variable of psychomotor retardation, or inhibition of crying, may be used for the prediction of elevated hydrocortisone levels, and (b) when protein-bound iodine levels are predicted, multiple factors should be used for weighting the prediction.

On the subsequent occasions of testing the ratings of depression, hydrocortisone and PBI levels fall. However, this was not true of the EST group, and an explanation is suggested for the relationship of function of the adrenal cortex and the thyroid in depression.

(Authors' Abstr.)

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*Effects of Induced Hyperthermia on Some Neurological Diseases*

A series of 100 subjects, 16 normal persons and 84 patients with neurological diseases, were immersed in water at 104 to 110°F. and observed for neurological changes.

There were 2 instances of tetany, manifested by carpopedal spasm, hyperactive reflexes, and a positive Chvostek sign, and 1 instance of decreased grip strength in the 16 normal subjects who were immersed.

Each of the 12 patients who had multiple sclerosis developed neurological changes, which occurred more frequently and, in general, at a lower elevation of body temperature than in patients with other diseases of the nervous system.

The appearance and disappearance of neurological signs often paralleled the rise and fall of body temperature in patients with multiple sclerosis, but changes occasionally occurred without any elevation in body temperature.

Because patients with multiple sclerosis can develop serious neurological dysfunction on exposure to heat, they should avoid excessive heat, especially hot baths.

Of a group of 72 patients with diseases of the nervous system other than multiple sclerosis, 40 showed significant neurological changes. These were the development of, or intensification of, nystagmus, in 24 patients; appearance of visual field changes, in 4 patients; change in the ankle jerk, in 10 patients; decrease in grip strength, in 10 patients; appearance of seizures, in 3 patients; change in the plantar response, in 3 patients, and decrease in visual acuity, in 2 patients.

Mental changes were observed in both the intact and the patient groups, but more frequently in the latter, and especially so in patients with multiple sclerosis.

Nine of twelve patients with multiple sclerosis developed the syndrome of dysfunction of the medial longitudinal fasciculus. Six of these had predominance of nystagmus in the abducting eye prior to the appearance of other parts of the syndrome. Such changes were not seen in the 72 patients with other diseases of the nervous system.

Nine patients with multiple sclerosis developed nystagmus or showed an intensification of pre-existing nystagmus; five showed a decrease in visual acuity; one showed a decrease in grip strength, and one developed a change in the plantar response. Such changes were also seen in 40 of a group of 72 patients with other diseases of the nervous system.

(Authors' Abstr.)

*Narrowed Attention*

A psychiatric, psychological, and social study of 45 randomly selected and representative surgical patients 65 years and over is reported.

1. Deterioration of mental capacity progressed in 11 cases during their hospital surgical treatment. The following aetiologic factors were significant:

- (a) Patients of 70 and over were more liable to progression of mental deterioration.
- (b) The acute brain syndrome or delirium preceded chronic deterioration in seven cases.
- (c) Antecedent anxiety, depression, and severe emotional disturbances were associated with later deterioration in nine patients.
- (d) Patients who had lost an accepting and comfortable home environment were more liable to deterioration.

2. Depression of a disabling kind appeared in 22 of the total 45 cases. This affect was forced by a complex combination of psychodynamic factors, including perception of lack of capacity to resist everyday stress, hostility and guilt, perception of defect in body image, loss of self-esteem, impairment of ability to remain active, and threat to self-preservation.

3. Projection and paranoid ideation were significant psychopathologic phenomena in nine cases. Principally, this reaction occurred in response to the real or imagined indifference of those persons significant to the elderly patient.

4. Two over-all responses of the aged to surgery are described, the reactions of "renewal" and "depletion". Renewal is intended to characterize a self-concept of repair, hope, and freedom to continue activity and a capacity to invest affect outside the individual. Depletion is intended to characterize an awareness or half-awareness of a sense of personal deterioration, with lessened capacity to meet stress and a need to draw resources inward, to withdraw, and to mobilize for self-preservation. It is theorized that the psychodynamic effect of the reaction of depletion has pathophysiologic consequences.

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### *Lysergic Acid Diethylamide (LSD-25) Antagonists*

The effect of 1-methyl-d-lysergic acid diethylamide (MLD-41) has been studied in the Siamese fighting fish and in man.

MLD-41 affects both the Siamese fighting fish and man similarly to LSD-25 (d-lysergic acid diethylamide). However, there are important differences; in the fish it is about one-tenth as effective as LSD-25, and in man the threshold of response is two to three times as high. In the non-psychotic test group studied, the threshold was approximately 70  $\mu$ g when taken orally.

Tolerance development to LSD-25 was achieved by administering MLD-41 for five to six days before administering LSD-25. The experiments reported indicate that approximately 100  $\mu$ g. of MLD-41, administered with increasing doses to 350  $\mu$ g. on the last day, protects against 100  $\mu$ g. of LSD-25 taken orally.

BOL-148 (2-bromo-d-lysergic acid diethylamide) produces tolerance to LSD-25, but the effect for equal weights is much less, approximately one-third that of MLD-41.

The implication of the rapid and effective development of tolerance to LSD-25 by MLD-41 is considered in relationship to a chemical theory of the schizophrenias and the possibility of therapy if the chemical theory is validated.

(Authors' Abstr.)

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### *Studies with Ceruloplasmin and a New Hallucinogen*

A recently synthesized atropine-like compound, N-ethyl-3-piperidyl benzilate, induced altered feeling states, visual and auditory hallucinations, and increased serum ceruloplasmin in seven of nine patients.

Infusion of four pyrocatechol amines—epinephrine, levarterenol, isoproterenol, and serotonin—appeared to have no effect *per se* on serum ceruloplasmin. Iproniazid, an amine-oxidase inhibitor, was likewise ineffective.

Serum ceruloplasmin undergoes small, but significant, increases during psychiatric disturbances of neurotic type and proportions, and decreases by a similar amount during periods of tranquility.

(Authors' Abstr.)

### *Urinary Excretion of Some Products of Tryptophan Metabolism in Schizophrenic Patients*

A chromatographic method for the qualitative determination of hydroxylated products of indole metabolism is described. The method is applied as a pilot study of the urinary excretion of hydroxylated indoles in schizophrenic and non-schizophrenic subjects. Results

indicate that a hydroxylated indole or tryptophan derivative which does not appear to be either 5-HIAA or 5-HTA is deficient or in low concentration in the urine of schizophrenics. Additional control measures and quantitative techniques must still be employed before the observed differences can be properly evaluated.

(Authors' Abstr.)

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*Relation of Emotional Responses and Changes in Plasma Hydrocortisone Level after Stressful Interview*

The present report has attempted to investigate the relationship between emotional response and the plasma level of hydrocortisone under the impact of a stressful interview. Two major areas of psychological-endocrine interaction were examined: (1) the effect of emotional response and (2) the effect of the psychological stimulus on the change in the hormone level. The degrees of increase in anxiety, anger, depression, and a combined affect rating were found to be significantly and linearly related to the change in the plasma hydrocortisone level. This relationship was maintained even though the affect change was rated for only a short time period. It would appear that the plasma level of hydrocortisone is increased by any type of emotional arousal. However, data were presented which indicated a particularly striking effect when anxiety of a disintegrative nature was developed in the course of the stress interview. Stimulus-hormone relationships were also found to occur, but these relations were generally less striking than response-hormone relations. The stresser's attitude and his total stimulus intensity rating tended to parallel the change in plasma hormone level. A significant stimulus-hormone relationship occurred when the stimulus produced a relatively intense emotional response in the subject. The findings presented are of special interest because this experiment included only a moderate range of emotional responses. The limited data available on more extreme responses suggest that an even greater degree of adrenocortical activation occurs.

(Authors' Abstr.)

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*Memory Deficit Produced by Bilateral Lesions in the Hippocampal Zone*

Bilateral removal of the hippocampus and hippocampal gyrus in man produces loss of recent memory. As soon as he has turned his attention to something else, the patient is unable to remember what was happening a moment earlier. It is as though he had made no record of present experiences. He also had a retrograde memory loss that covers a considerable period before operation.

This is a confirmation of the suggestion of Glee and Griffith, based on the evidence of autopsy study of a patient with bilateral brain lesions. "The suggestion is made", they wrote,



"that the hippocampal formation of the adult seems to be essential for recent memory". In their case, as well as in the authors' cases, the hippocampal gyrus was destroyed along with the hippocampus.

Psychological study of the authors' patients shows that, in spite of the above-noted deficiencies, memory for the distant past is not lost, nor is there corresponding loss of attention, concentration, reasoning ability, or previously acquired skills. The intelligence quotient shows no drop when compared with pre-operative testing. There is no interference with speech, and the memory of words is unimpaired.

It may be concluded that an essential part of the recording mechanism is contained in the hippocampal zone. Certainly, also, another part of the mechanism lies in the central integrating circuits of the brain stem, circuits that have duplicate connections with the two hippocampal areas.

These conclusions are based largely on the post-operative study of four patients in whom this distressing complication appeared. Two of the patients were found to have this defect after unilateral excisions had been carried out in the treatment of temporal lobe epilepsy, the contralateral hippocampal zone apparently having been injured by incisional herniation at birth. Two patients were added, for the authors to study, in whom bilateral hippocamp-ectomy had been carried out by Dr. William Scoville, in his search for a better operation to replace frontal lobotomy, as a treatment for hopeless psychotics. The symptom complex was identical in all four.

This case analysis was undertaken originally because of remorse that two of the patients should have suffered a complication. It is a severe handicap to them, although both continue to earn their living, which had been threatened by the frequency of their pre-operative cerebral seizures. But the study, which was intended primarily to serve as a warning so that others, as well as the authors, might avoid this pitfall, has opened up new and exciting evidence.

Neurosurgeons who hope to cure temporal-lobe seizures by removal of one anterior temporal lobe and all of the hippocampal zone should bear in mind that the squeezing of the baby's head at the time of birth, which produces temporal herniation and incisional sclerosis, may occasionally destroy the hippocampal zone on one side and injure that zone on the other. Thus the major epileptogenic discharge may be on the side of the less severe injury. Removal of the zone on that side might then be expected to result in this loss of recent memory. Such a loss is what occurred in the two cases that have been reported.

The authors have carried out careful psychological study of more than 90 other patients before and after the same unilateral operation, and they showed no evidence of general memory loss. Under normal conditions one hippocampal area duplicates the work of the other and carries on when one is removed.

For the time being, in order to guard against such memory losses, we have adopted the policy that when the initial electroencephalographic study points to independent abnormality in both inferior temporal regions, no removal should be made of either hippocampal zone.

The analysis of this complication of recent memory loss, undertaken as a neurosurgical project, has thrown welcome light on the location of some portion at least of the ganglionic record of current experience. It has demonstrated that this record is anatomically separate from the neurological mechanisms that are related to words, skills, and concepts that have been previously acquired.

(Authors' Abstr.)

#### *Effect of Hypothalamic Lesions on the Amygdala Syndrome in the Cat*

In the cat the "amygdala syndrome" does not appear after bilateral ablation of the amygdaloid complex if there has been previous destruction of the ventromedial hypothalamic nuclei or the mammillary bodies; and the amygdala syndrome, once produced by the amygdala ablation can be abolished by the hypothalamic lesions. Examples of lesions and theoretical considerations are included.

(Authors' Abstr.)

#### *Studies in the Effect of Lysergic Acid Diethylamide (LSD-25)*

Under the influence of lysergic acid diethylamide (LSD-25), for both normals and schizophrenics, there is a significant increase in the perceived size of one's own body and its parts, and no significant change in the perceived size of external objects. These findings are interpreted in terms of the assumption that LSD operates as a primitivizing agent, which is assumed to lessen the definiteness of the boundary of the body in relation to the surroundings.

(Authors' Abstr.)

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*Parkinsonism, Schizophrenia and Ataractic Drugs*

The appearance of the neurological symptoms of parkinsonism in ataraxic patients is usually regarded as an undesirable "side-effect". The true significance of parkinsonism, however, becomes evident when its psychological symptoms are also taken into account. While these characteristic mental signs—bradyphrenia and emotional indifference—are probably closely related to the therapeutic effect of the ataractic drugs it is believed that the neurological symptoms of parkinsonism are not undesirable in themselves. They may require specific, additional medication, but their appearance indicates that a therapeutic dosage has been reached.

In using the parkinsonian effect of ataraxics as a basis, an attempt is made to illustrate the close relationship between schizophrenia and extrapyramidal system.

(Author's Abstr.)

*Phrenotropic Action of Methylphenidylacetate (Ritalin)*

Improvement following Ritalin therapy ranged from better self-care to restoration to active and substantially normal life outside the hospital. Verbalization was restored and/or normalized, and many patients reported feeling more "alive", "interested" or "normal" than for a long time. Delusional and hallucinatory trends were greatly reduced. Physical and mental lethargy caused by necessarily large doses of various ataraxic or anticonvulsant drugs responded well to Ritalin, as previously reported by Ferguson and Carter and further confirmed by Lazarte and Petersen. The writer has commented on several of these points previously, and feels that the findings in the series now being reported reinforce the earlier impressions. Carter also reported no deleterious effect of Ritalin in patients with pre-existing convulsive disease. In cases of chronic brain syndrome associated with senile disease confusion was lessened and alertness increased. In those with chronic brain syndrome associated with cerebral arteriosclerosis, orientation and clarity of thinking improved.

While Ritalin may produce hyperactivity requiring reduction of dosage or discontinuation, usually this can be controlled by reserpine, chlorpromazine or meprobamate, and there is no evidence thus far that it will aggravate pre-existing convulsive disease. This drug rarely produces a significant increase in normotensive or already hypertensive blood pressure, but in an occasional case such as the arteriosclerotic patient cited it may be contra-indicated.

(Author's Abstr.)

*Subcortical Functions of Tridione and Desoxyn in Mental Illness*

Recent work in neuropsychology is reviewed, with reference to the Papez circuit and the "Visceral Brain" which is proposed as the anatomical substratum of the subconscious mind. Correlation of clinical syndromes with the effects obtained by stimulating centres along the Papez circuit in the hippocampal formation, fornix, hypothalamus, and cingular gyrus is offered.

Clinical work with Tridione and Desoxyn is reported in a series of 16 patients. Dramatic recoveries and improvements have occurred in 11 of these severely ill psychotic patients.

As a working hypothesis, it is assumed that all motor nerve impulses arising in the central nervous system must find some effector pathway. If the original intention is repressed, a pathway is found to make a muscle move, a gland secrete, or a control centre to function.

Anatomical divisions and physiological responses in the central nervous system suggest that man has two brains working antagonistically and synergistically; one the neocortex, the other the visceral brain, composed of limbic lobe with its cingular gyrus, Island of Reil, claustrum, basal ganglia, amygdala, hypothalamus, and hippocampal formation.

(Author's Abstr.)

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*Frontal Leucotomy and Its Congeners*

With the numerous operative procedures described by the author, it would seem that after maybe another twenty years the choice would narrow down. But since surgeons are by nature inventive, it seems more probable that additional measures for producing lesions in various areas will be described. The really remarkable thing, however, is that every described operation can be counted upon to produce exactly the proportion of responses that Moniz reported in his first monograph in 1936, one-third recovered, one-third improved and one-third unimproved. Results are better or worse depending more upon the choice of the patient and less upon the choice of operation.

(Author's Abstr.)

*A Comparative Study of Modified and Unmodified Electric Shock Treatment*

The results and complications of modified and unmodified shock treatment, and patients' attitudes toward each, were compared in groups of subjects randomly selected for each treatment. The results of the two treatment methods were not significantly different. There were also few differences in patients' attitudes toward the two procedures. Complications, however, were more frequent among patients given the unmodified treatment than among those given the modified treatment. Restlessness just after treatment was also more common with the unmodified method. It was concluded that modified shock treatment is the method of choice.

(Author's Abstr.)

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*Effect of Rauwolfia Alkaloids and Related Substances on Chromatophores*

It is shown that those *Rauwolfia* alkaloids which are hypotensive and sedative to man in small dosage, namely, reserpine, raunormine and rescinnamine, and which have been shown to be releasers of serotonin, catechol amines and histamine in large dosage, are potent dilators of fish chromatophores in extreme dilution. This response of the fish melanophores is highly specific with respect to the drug causing the response, the cells which respond, and the class of vertebrates whose cells react. There is a local action in innervated cells. A general action is suggested, possibly via hypophyseal hormonal release.

(Author's Abstr.)

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*Recovery from Insulin Coma and Hematoencephalic Exchange*

In deep insulin hypoglycemia rabbit brain loses approximately fifty per cent. of its normal content of free glutamic acid. Glutamic acid administered either intravenously or subcutaneously will restore the level of free glutamic acid but the cortical electroencephalogram does not return to normal. Glucose alone given intravenously increases the free glutamic acid in the brain and the normal pattern of the cortical electroencephalogram returns. From this the authors draw the following working assumptions: (1) that the free glutamic acid used by the brain during deep insulin hypoglycemia does not yield sufficient energy to maintain the cortical electroencephalogram; (2) administered glutamic acid enters the brain more freely in the animal subjected to deep insulin hypoglycemia than in the normal rabbit but does not influence significantly the electrical activity of the cortex; (3) treatment with glucose restores the glutamic acid level and the electrical activity.

(Authors' Abstr.)

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Effects of Lobotomy in Childhood

Although lobotomy is an irrevocable and drastic procedure, the authors' twelve cases were such severe chronic problems that the only alternative to attempted relief of symptoms was custodial institutional care. The follow-up would seem to have justified the operative procedure. It could have been argued that growth may have accounted for the improvement. However, two or three facts argue against this. (1) Most cases of chronic childhood schizophrenia have not shown improvement. (2) The post-encephalitic cases have not improved. (3) The experience with hemispherectomy has shown that severing of brain connections has brought about marked satisfactory reduction or disappearance of behaviour disorders even of severe abnormalities of behaviour.

(Authors' Abstr.)

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#### *A Method for Differential Diagnosis of Brain Damage in Adolescents*

On the basis of age and sex differences, nine of the thirteen ratios originally presented by Hewson were modified and successfully used to differentiate organic and non-organic adolescent subjects.

Among the 160 control subjects (40 of each sex in a young and in a late adolescent age range), 92 per cent. had non-organic summary diagnoses according to the adolescent ratios. Hewson's original ratios yielded only 73 per cent. non-organic diagnoses for this group. Of the 40 experimental subjects, 100 per cent. of those who had positive neurological diagnoses had organic diagnoses according to the adolescent ratios. Only 80 per cent. of these subjects had organic diagnoses when Hewson's original ratios were used. In the group who showed no residual neurological impairment, 38 per cent. of those suspected of organicity had organic diagnoses according to both Hewson's and the adolescent ratios. In the remaining subjects who showed no residual neurological impairment but who had convulsive disorders, 67 per cent. had organic diagnoses according to the adolescent ratios while only 16 per cent. were classified as organic by Hewson's original ratios. Relationships between the present I.Q. and the age of the subject at the time of injury indicated that early injured subjects had lower I.Q.s than did later injured subjects.

(Authors' Abstr.)

#### *Seizures with Promazine*

1. Twenty-one chronic psychotic patients were given promazine over an average period of 68 days, with maximum doses ranging from 100 mg. to 1,800 mg. a day.

2. Of this group, six patients experienced a total of 11 grand mal seizures during promazine therapy. All these patients were receiving 900 mg. daily or more at the time of the convulsions.

3. Five patients also administered 900 to 1,500 mg. a day did not have seizures during therapy.

4. No patient of the 10 receiving less than 900 mg. daily had fits.

5. In three patients with clinical fits with promazine, serial EEG tracings showed paroxysmal records during drug use only; in two others with seizures, a normal record was found with and without the drug.

6. It is concluded that in this series the administration of high doses of promazine was associated with the occurrence of grand mal convulsions.

(Author's Abstr.)

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#### Experience with "BGE", A Naturally Occurring Indole Compound

"BGE" occurs during the intermediate metabolism of tryptophane in microbes. It can be isolated from mycelium of the mould *neurospora crassa*. It also occurs in pathological human urine. A substance apparently identical with "BGE" is formed by the action of hydrogen peroxide, cortisone or ascorbic acid on tryptophane, and is probably tryptophane with a hydroxyl group at the beta position and indole double-bonded shifted to the indolenine position. The compound is easily oxidized to beta-OH-oxindole-alanine. Oxindole-alanine is a component of the toxin of the fungus *amanita phalloides*. BGE is present in high amounts in all fast-growing cells, i.e. in human carcinoma tissue and also occurs in the urine of persons suffering from bacterial infections. The ingestion of cortisone markedly decreases the urinary secretion of indole-acetic acid, while BGE appears in high amounts. The author found that the ataractic drugs, reserpine, Frenquel and chlorpromazine, all interfere with tryptophane metabolism, and are to be regarded as metabolic poisons. The author found that chemical manipulation of BGE gave rise to fumes which produced in him psychotic symptoms much resembling those from mescaline and LSD-25. These symptoms were relieved within half-an-hour by a 100 mg. tablet of Frenquel.

G. W. T. H. Fleming.

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*Lactic Dehydrogenase of Cerebrospinal Fluid in the Differential Diagnosis of Cerebrovascular Disease and Brain Tumor*

The concentration of the enzyme, lactic dehydrogenase, has been examined in spinal fluids from a series of patients with a variety of disorders. Significantly higher enzyme levels have been found in the cerebrospinal fluid of patients with cerebrovascular accidents as compared with normal individuals and patients with neurological disease including brain tumor. The test is suggested as useful in the differentiation of cerebrovascular accident from other disease with similar clinical picture.

(Authors' Abstr.)

## MARCH

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## Symposium on Head Injuries: Physiological Basis of Concussion

1. Since the effects of mechanical alterations at the moment of impact in head injury must ultimately be reflected by alterations of the properties of neuronal membranes, this has been studied by recording the electrical activity at various levels of the nervous system.
2. Whereas there may be surprisingly little change in the spontaneous electrical activity of the cerebral cortex and many subcortical structures, there is consistent reduction of activity in the reticular formation of the mid-brain following a concussive blow.
3. Whereas there is no alteration of conduction of sensory impulses over the classical sensory pathways to thalamus and cortex, evoked sensory responses in the reticular formation are blocked or markedly attenuated by concussion.
4. Since it is known that such sensory driving of the reticular activating system is necessary to maintain consciousness, the genesis of coma following head injury would seem to be on this basis.
5. These alterations of properties of neuronal membranes following concussion may be related to biochemical alterations, including the metabolism of acetylcholine, which are known to follow concussion.

(Authors' Abstr.)

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*The Spiral After-effect and Reversible Figures as Measures of Brain Damage and Memory*

A group of 32 brain-damaged adolescent boys (CBS) and a group of 35 emotionally disturbed non-psychotic boys (ED) of equated age were administered the spiral visual after-effect (SVA), two reversible figures, and a memory paragraph for immediate and delayed recall.

A significantly greater percentage of the brain-damaged group did not perceive SVA, and the duration of SVA for this group was significantly longer than for group ED. Rate of reversals for both reversible figures was significantly lower for group CBS, and a significantly smaller percentage of group CBS reported reversals spontaneously. No relationship was obtained between SVO and reversible figures.

For both immediate and delayed recall, group ED was significantly superior. There was no significant difference in memory loss over time. The duration of SVA showed a significant negative relationship to the measure of immediate recall, and the rate of Necker Cube reversals was significantly related to the measure of memory loss over time. No other correlation between memory, SVA, reversible figures, and groups was significant. The possibility that the two significant findings might be spurious is discussed.

The data are viewed in relation to diagnostic problems, recent theorizing about cortical functioning, and the possibility of further refinement of the SVA procedure.

(Authors' Abstr.)

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*Distribution of Carbon-14 Labeled Isoniazid in Brain*

1. The distribution pattern of carbon-14 labeled isoniazid in the central nervous system of cats was determined by radio-assay of dissected tissue samples and auto-radiography at several time-points following injection of the drug. A well defined and consistent pattern of distribution from animal to animal was revealed.

2. Attempts to relate the local concentration of carbon-14 label to local vascularity in the central nervous system disclosed general agreement for some areas, but gross inconsistencies in others. The labelled drug was present in high concentration in hippocampus despite relatively lower vascularity, while the opposite was true in the geniculate bodies and inferior colliculi which are regions of high vascularity in the cat.

3. Hippocampus was unusual in another respect in that the relative concentration remained high throughout 12 hours, while the relative concentration in other areas of brain was falling.

4. It is concluded that factors other than local vascularity condition the distribution of this drug in the central nervous system of cats. These factors are not understood at present.

(Authors' Abstr.)

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| *A Study of Cholinesterase and Ali-esterase in Various Neurologic Diseases. <i>Bernsohn, J., et al.</i> .. ..                   | 221 |

*Celontin in Patients with Refractory Epilepsy*

Sixty-two epileptic patients with various types of seizures previously partially or totally refractory to former anticonvulsant therapy were treated with Celontin (N-methyl-a, a methylphenylsuccinimide) in doses up to tolerance. In nearly all instances, the new drug was added to or replaced part of the previous maintenance medication. Of the 54 patients who received Celontin long enough for adequate evaluation, six patients achieved complete seizure control, six were distinctly improved, and five patients experienced an increase in seizure frequency on the drug. The remainder noted little or no improvement. Age, clinical seizure type, and electroencephalograph pattern bore little relation to the level of improvement. Principal side effects were sedation and ataxia, usually related to over-medication with Celontin or additive effect of Celontin with other anticonvulsant agents. Two patients demonstrated evidence suggestive of liver damage. Six patients noted undesirable psychic reaction, in two instances requiring hospitalization. Periorbital oedema occurred in three patients, albuminuria in one, and skin rash in two individuals. Other side reactions were minor and transient.

It is felt that this drug is a useful addition to the therapeutic armamentarium against the epilepsies, particularly in patients with residual abortive or minor seizures subsequent to fair control of major attacks.

(Authors' Abstr.)

*A Study of Cholinesterase and Ali-esterase in Various Neurologic Diseases*

1. The true-cholinesterase, pseudo-cholinesterase, and ali-esterase activities of cerebrospinal fluid in 159 patients with various neuropathologic conditions were determined. The two cholinesterases were estimated by their activity on the same substrate, acetylcholine, and differentiated by the use of Mytelase, a specific true-cholinesterase inhibitor.

2. In the studies in multiple sclerosis, hemiplegia after cerebrovascular accident, epilepsy, myasthenia gravis, and Guillain-Barré syndrome, a wide range of activity was evident for the three enzymes studied. Cerebrospinal fluid was found to contain an active ali-esterase, using phenyl acetate as a substrate.

3. A high true-cholinesterase activity was found in seven cases of myasthenia gravis, one of cortical atrophy, and one of porphyria.

4. No evidence of any deviation in pseudo-cholinesterase or ali-esterase activity was evident in the spinal fluid in multiple sclerosis.

5. A difference in ali-esterase activity in cases of epilepsy from organic causes as compared to the idiopathic form was observed.

6. A high ali-esterase activity was found in the Guillain-Barré syndrome, which was correlated with the high albumin fraction in cerebrospinal fluid.

(Authors' Abstr.)



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*The Action of Autonomic Drugs on Normal Persons and Neuropsychiatric Patients: The Role of Age*

In experimental studies on cats it has been shown in the authors' laboratory that simple autonomic tests reveal the state of excitability of the hypothalamus. The degree of the hypotensive action of Mecholyl indicates the state of sympathetic hypothalamic excitability, whereas the pulse-slowing reflex induced by the rise of the systolic blood pressure upon intravenous injection of norepinephrine indicates the state of parasympathetic hypothalamic excitability. The application of these tests in normal persons and neuropsychiatric patients shows:

1. The sympathetic excitability declines progressively with increasing age in normal individuals and mental patients. This decline is independent of changes in the blood pressure level since it occurs in groups of persons whose mean blood-pressure is practically the same in the three age groups studied.

2. In view of the considerable influence exerted by the age factor on the sympathetic excitability indicated by the Mecholyl test, a comparison between normal persons and groups of patients is valid only when similar age groups are compared. Significant differences exist between the control and the mental group under these conditions. At all ages the sympathetic hyper-reactors and hypo-reactors are in the majority in the group of mental patients, whereas they are in a minority in the control group. Sympathetic hypo-reactors are present in schizophrenics at the age of 25 and less but are absent in the control group.

3. Somatic therapy is recommended in functional mental disorders with the view to restoring physiological autonomic excitability at the hypothalamic level. This recommendation

is based on four groups of data showing that (a) the Mecholyl test indicates sympathetic reactivity at the hypothalamic level; (b) autonomic changes indicated by the reaction to Mecholyl are paralleled by changes in behaviour (Funkenstein *et al.*); (c) procedures such as electroshock, which according to the physiological analysis increase central sympathetic reactivity, benefit patients who are sympathetic hypo-reactors but not sympathetic hyper-reactors; (d) procedures such as the inhalation of high concentrations of carbon dioxide, which has been shown to diminish the reactivity of the sympathetic division of the hypothalamus and the intensity of the hypothalamic-cortical discharge, are beneficial in the treatment of sympathetic hyper-reactors but are contraindicated in the case of sympathetic hypo-reactors.

Statements (c) and (d) refer to the clinical work of Funkenstein *et al.*, and Moriarty, respectively, and the physiological work elucidating the nature of the Mecholyl test. The therapeutic effect of carbon dioxide therapy was predicted in 1953.

4. The quotient:

|                                             |
|---------------------------------------------|
| Maximal rise of the systolic blood pressure |
| Maximal diminution of the heart rate        |

following the intravenous injection of 0.005 mg. norepinephrine has been used as an indicator of parasympathetic hypothalamic excitability, since physiological work showed the dependence of this quotient on the excitability of the anterior hypothalamus. This quotient showed variations too great to permit the recognition of any difference between the control group and the neuropsychiatric group. However, the work showed that the parasympathetic reactivity declines in the normal and abnormal groups with increasing age.

Increasing age is, therefore, associated with a decrease in sympathetic and parasympathetic central reactivity. Whether the state of autonomic balance changes with increasing age cannot yet be said.

(Authors' Abstr.)

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1. The effect of the ingestion of a 20 per cent. alcohol solution as the sole source of fluid on glutamic pyruvic and glutamic oxalacetic transaminase activity in rat livers has been compared with pair-fed, isocaloric and pair-fed, and ad lib-fed controls, under conditions of varying food intake, in two experiments. All animals received adequate amounts of lipotropic factors and vitamins throughout.
2. At 24 weeks the hepatic GOT/GPT ratio was significantly higher in the alcohol-fed group, as compared with the pair-fed water-fed controls.
3. In both experiments there was a diminution in hepatic GPT activity in the alcohol-fed group at 8 weeks as compared with any of the controls, a change which was independent of calorie intake. This change was not observed in brain.
4. Upon starvation there was a significant increase in hepatic GPT activity in the alcohol-fed group and the pair-fed controls only.
5. These changes are interpreted as indicating a direct effect of alcohol on the liver of rats.

(Authors' Abstr.)

*Treatment of the Acute Alcohol-Withdrawal Syndrome*

An outline of medical therapy for the acute alcohol-withdrawal syndrome has been presented. It is based on the clinical impression, supported to some extent by laboratory observations, that the alcoholic, during withdrawal, suffers from acute dehydration and acute starvation, and is in need of sedation. Intravenous glucose, salt and water are given, and sedation is achieved primarily with chlorpromazine. By immediately attending to these three primary factors—dehydration, starvation, and need for sedation—the withdrawal period is shortened, complications are minimized, the need for prolonged sedation is eliminated, and nursing care is made easy. The average physician, without extensive experience with alcoholism, is given a safe method of handling the acute withdrawal syndrome in a general hospital.

(Author's Abstr.)

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